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MEDICAL AND SCIENTIFIC ASPECTS  
OF  
THE DEFENSE  
OF  
RESPIRATORY CANCER LAWSUITS

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**MEDICAL AND SCIENTIFIC  
ASPECTS OF THE DEFENSE OF  
RESPIRATORY CANCER LAWSUITS**

**Table of Contents**

- I. Introduction**
- II. Nature of Cancer; Glossary of Terms**
- III. Biographies**
  - A. The Proponents of the Respiratory Cancer-Tobacco Smoking Theory**
  - B. The Opponents**
- IV. Tobacco Smoking and Respiratory Cancer**
  - A. Earliest Charges Against Tobacco**
  - B. Statistical Studies**
    - 1. Types; Characteristics**
    - 2. Individual Studies**
      - a. Retrospective**
      - b. Prospective**
        - (i) Hammond and Horn**
        - (ii) Doll and Hill**
        - (iii) Dorn**
    - 3. Summary of Statistical Studies**
    - 4. Criticisms of Statistical Studies**
      - a. Selection Bias**
      - b. Accuracy of Information (Diagnosis);  
Accuracy of Information (Smoking Habits)**

2025018053

- c. Other Noteworthy Criticisms of the Statistical Studies
- d. Other Factors Not Studied, or if Studied, Not Sufficiently Emphasized
  - (i) Urban-Rural
  - (ii) Male-Female Ratio
  - (iii) Constitutional Hypothesis
  - (iv) Multiple Causes - If Tobacco Smoke Causes Lung Cancer, Is It the Only Cause?
- e. Is the Claimed Increase in Lung Cancer Incidence Real or Illusory?
- 5. Past Medical Blunders of Association
- 6. Miscellaneous
- 7. Summary of Criticisms
- C. Biological Studies on Tobacco Products
  - 1. The Role of Animal Experimentation in Cancer Research
  - 2. Skin Painting Experiments Using Tobacco Products
    - a. Positive Results
    - b. Negative Results
      - (i) Mouse Painting and Ingestion
      - (ii) Embryonic Tissue Transplants
      - (iii) Other Test Animals
  - 3. Experiments with Regard to the Lung and Other Sites
    - a. Inhalation Experiments
    - b. Direct Application

D. Chemical Studies on Tobacco Products

1. Polycyclic Hydrocarbons
2. Arsenic

E. Summary

V. Environmental Factors in Respiratory Cancer Causation

A. Atmospheric Pollution

1. Introduction
2. Epidemiological Studies
  - a. Human
  - b. Other Species
3. Biological Studies
  - a. Skin Experiments
  - b. Inhalation Experiments
4. Chemical Studies
  - a. 3,4-Benzpyrene
    - (i) Demonstration of Its Presence in Various Pollutants
    - (ii) Demonstration of Its Presence in the Atmosphere of Various Areas
  - b. Other Polycyclic Hydrocarbons
  - c. Oxidized Aliphatic Compounds
  - d. Nitrogen Oxides
  - e. Arsenic
5. Summary

**B. Occupational Exposures****1. Inorganic Chemicals**

- a. Nickel
- b. Chromium
- c. Arsenic
- d. Iron
- e. Beryllium

**2. Organic Chemicals**

- a. Combustion and Distillation Products of Coal
- b. Petroleum, Shale Oil and Natural Gas

**3. Polymeric Material**

- a. Asbestos
- b. "Isopropyl Oil"

**4. Irradiation****C. Geographic Factors****D. Socio-Economic Factors****E. Summary****VI. Pathogenesis****A. Observations of Changes in Respiratory Cell Structure and Interpretations of the Meaning Thereof**

- 1. Auerbach et al.
- 2. Black and Ackerman
- 3. Chang

4. Chayen et al.
5. Hamilton et al.
6. Hilding
7. Kotin et al.
8. Sanderud
9. Szolomajer
10. Weller
11. Wittekind and Struder
12. Some Recent Studies

- B. Experimental Carcinogenesis
- C. Summary

#### VII.. The Possible Role of Viruses in Cancer Causation

- A. Necessity for Indirect Approach to Cancer Causation
- B. Chronological Review of Virus/Cancer Relationship
- C. Malignant Viral Tumors
- D. Extrapolation to Man
- E. Latency in Some Cases
- F. Discovery of "Virus-Like" Particles in Human Cancers
- G. Effect of Addition of Chemical Substances
- H. Summary

#### VIII. Opinions of Government Agencies and Various Medical Societies, Groups, Etc.

#### IX. Summary

Bibliography

Index

**Appendix**

**Outline of Cross Examination of Expert Witnesses:  
Basis of Opinion**

- A. Statistical Studies**
- B. Animal Experiments**
- C. Physiological Studies**
- D. Alleged Carcinogenic Agents in Cigarette  
Smoke**

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MEDICAL AND SCIENTIFIC ASPECTS OF THE  
DEFENSE OF RESPIRATORY CANCER LAWSUITS

I. INTRODUCTION

In 1950, Wynder and Graham (474) released the results of a retrospective statistical study on the effect of smoking on lung cancer. The authors concluded from their data that tobacco smoking, and in particular, cigarette smoking, was one of the major causes of the high incidence of cancer of the lung in the American male. Since 1950 there has been a constant barrage of statistical, biological and chemical publications in the scientific and medical literature, all purporting to provide further evidence on the question whether cigarette smoking is a major etiological factor in respiratory cancer causation. The bulk of this literature has become tremendous during the past decade and some 6000 articles on the effect of smoking on some phase of health have been abstracted by Rodgman during the past five years. It is estimated that well over 60 percent of these publications concern some phase of the lung or laryngeal cancer problem. Most of the remainder are concerned with circulatory and heartdisease. Presently, the mass of literature is being expanded at the rate of at least one hundred articles per month.

As a result of this tremendous wealth of

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material, many medical and scientific investigators have become convinced that cigarette smoking is an important factor in lung cancer causation. On the other hand, there are many scientists, probably fewer in number, who are equally convinced that the data amassed to date are not as yet definitive. Unfortunately for the Tobacco Industry, the proponents of the lung cancer-cigarette smoking theory have been able to wage an effective propaganda campaign. This propaganda campaign has planted in the lay press many statements and opinions concerning the lung cancer-smoking controversy that are not based on sound scientific facts. Possibly as an outcome, numerous suits have been brought against tobacco companies by smokers suffering from lung cancer or by the descendants of smokers dying from the disease.

Obviously, it is impossible for counsel representing a particular Tobacco Company to read through the great volume of material at hand re the respiratory cancer-tobacco smoking controversy on the basis of the time factor alone.

In an attempt to synthesize this material, we have summarized the opinions and results, both pro and con, of many of the prominent investigators involved in this controversy. Many of the publications which have appeared in the literature are not concerned with original research but are mainly reviews of or the expression of

opinions concerning results described by others. In the main, we have sought to present the results of original research only, together with pertinent comments or criticisms of these results when these were logically founded. This, in essence, is our purpose -- to describe for defense counsel the medical and scientific aspects of the defense of respiratory cancer lawsuits.

This paper borrows directly from the work of other counsel who have also prepared papers, for a similar purpose, on the subjects of statistical studies, and animal and chemical experiments. We are of course indebted to them for such assistance in putting together this overall picture of the medical and scientific literature.

The first part of this review consists of a brief discussion of the nature of cancer, descriptions of cells and the presentation of pertinent definitions.

The general plan of the balance is as follows:

- (a) Reference to some of the publications released prior to 1945 in which smoking was either mentioned as or supposedly shown to be a possible cause of cancer of the lung and/or larynx.
- (b) A brief description of the retrospective and prospective statistical studies which are considered by some to demonstrate conclusively that an association exists

between respiratory cancer and smoking. This description is only a summary of the findings and does not attempt to present in detail either the great number of tables recorded in the original publication or the methodology of the statistical manipulation involved.

- (c) An outline of the various criticisms of the statistical studies, and, where applicable, answers to and criticisms of these criticisms.
- (d) A summary of the biological and chemical investigations which are considered by some as ancillary evidence that the lung cancer or laryngeal cancer-cigarette smoke theory is valid. This section involves the results of animal experimentation, and the demonstration of known carcinogens, e.g., polycyclic hydrocarbons, arsenic, in tobacco smoke.
- (e) An outline of environmental factors suspected in the etiology of lung cancer will be presented. This section will deal with the epidemiological, biological and chemical data supporting the environmental factors -- respiratory cancer theory.

- (f) Pathogenesis of cancer will then follow, with particular reference to respiratory cellular changes attributed by some to exposure to atmospheric pollutants or tobacco smoke.
- (g) Several miscellaneous sections including viruses, etc. will follow.
- (h) A bibliography of all publications cited. The citations herein in parentheses following an author's name are in each case to the number arbitrarily assigned each paper by Rodgman in a series of Abstracts prepared by him from 1955 to date. The accompanying bibliography identifies these papers, listing them (1) in numerical order and (2) in alphabetical order according to the name of the author first shown on the paper.

(1) A subject index.

Examination of the Table of Contents will provide a more detailed description of the scope of this review. It is intended that periodically sections of the review will be amended as new information, arguments, opinions, etc. appear in the literature.

At this point, it may be opportune to present a list of some half dozen publications which will provide

the reader with a wealth of background material with respect to respiratory cancer causation and the cancer-cigarette smoking theory. These publications are as follows:

Bing, R.J., Dyer, R.E., Lilienfeld, A.M., Nelson, N., Shimkin, M.B., Spain, D. and Strong, F.F., The Relationship of Smoking to Cancer and Other Diseases. SCIENCE, 125, 1129-1133 (1957); also appeared in the New York Times, Mar. 23 (1957).

Cornfield, J., Haenszel, W., Hammond, E.C., Lilienfeld, A.M., Shimkin, M.B., and Wynder, E.L., Smoking and Lung Cancer: Recent Evidence and a Discussion of Some Questions. J. NATL. CANCER INST., 22, 173-203 (1959).

Doll, R., The Etiology of Lung Cancer. ADV. CANCER RESEARCH, 3, 1-50 (1955).

Hueper, W.C., A Quest into the Environmental Causes of Cancer. PUBLIC HEALTH MONOGRAPH, No. 36, Jan. (1956).

Kotin, P., The Role of Atmospheric Pollution in the Pathogenesis of Pulmonary Cancer: A Review. CANCER RESEARCH, 16, 375-393 (1956).

U. S. Govt. False and Misleading Advertising  
(Filter-Tip Cigarettes). Hearings before a  
Subcommittee of the Committee on Government  
Operations, House of Representatives, 85th  
Congress, First Session, July 18, 19, 23-26  
(1957).

Numerous other review articles could have been  
suggested but those cited are considered representative  
at the present time.

## II. NATURE OF CANCER; GLOSSARY OF TERMS

All living things consist of cells from the simplest forms of life, e.g., the amoeba, which are made up of a single cell, to the higher mammals, e.g., man, which contain millions of cells. The cells constituting the human body vary considerably in size but are so small that 700 to 800 would cover a pinhead. Each cell consists of a jelly-like body, the cytoplasm, surrounded by a membrane. The cell membrane is semi-permeable, permitting the passage of fluid and small particles into and out of the cell. The cytoplasm surrounds a dense globular structure called the nucleus which contains minute thread-like fragments called chromosomes. The chromosomes have numerous swellings, called the genes, and these in the case of the sex cells, e.g., spermatozoa and ova, contain the mechanism which determines such characteristics as complexion, hair and eye color, body build, and sometimes a tendency to certain diseases. All cells contain chromosomes and genes because, on special occasions, these cells must reproduce themselves even though they are not concerned with the formation of new individuals.

Some cells secrete fluid, e.g., saliva and mucus, and are called glandular cells. These cells

form cylindrical patterns somewhat resembling the stones or bricks in a wall. Cells of the skin (called epidermoid cells) form layers in sheets somewhat like an extended brick wall; whereas, nerve cells resemble minute telephone cables. Cells combine to form tissue which, in turn, arranges to form the various organs.

The evolution of the many types of body cells from a single cell is called differentiation, which begins with the division of the fertilized ovum into 2, then 4, 8, 16, etc., cells until a cluster is formed. This mass of dividing cells begins to organize while, at the same time, the cells begin to differentiate into classes to form the rudiments of the system of blood vessels, skeleton, digestive tract, etc. This process of cell reproduction, differentiation and organization continues until formation of the new organism is completed. In man, reproduction of highly differentiated cells is possible only to a limited degree in contrast with some of the lower animals, e.g., the salamander, which can replace in toto certain lost parts.

Thus normal growth can take place by development of new organisms, gradual replacement of aging cells and repair of damaged tissues. Abnormal



growth is an over-reproduction of cells without apparent purpose. To date, it is not known precisely whether abnormal growth is the result of reproduction of an abnormal cell, whose abnormality is produced by some external agent or process, or whether the abnormal cell is a product of the abnormal growth. Many authorities consider that the abnormal cell is first produced and this abnormality produces or results in rapid multiplication (abnormal growth).

Cancer may be considered in its simplest sense as the rapid and unrestrained multiplication or abnormal growth of an abnormal cell, this abnormality in the cell being caused by agent or agents known or unknown acting on the normal cell in an unknown manner. Also, this abnormality of the cell may not be too evident even on very rigid examination. This is particularly true in the case of benign tumors (see following). A cluster of these abnormal cells resulting from the multiplication of a single abnormal cell is called a tumor. The degree of departure from normality is constant for the cells of a particular type of tumor. Generally, the greater is the departure of the cell from the normal, the greater is its rate of growth [Haddow, Nature, 154,

194 (1944)].

Tumors may be classified into two general groups: benign and malignant. A benign tumor shows the differentiation common to normal tissue. It grows by expansion and at a relatively slow rate; its growth ceases after a time and complete regression is possible.

A malignant tumor is undifferentiated, grows rapidly by infiltration and metastasis, i.e., by the splitting of small groups of cells from the primary growth and transportation of these groups by the body fluids, such as the lymph and blood, to distant tissues where growths similar to the primary tumor result. It is frequently a matter of some difficulty to determine, even with the benefit of an extensive and careful autopsy, the site of a primary cancer. In general, the growth of a malignant tumor does not cease until the host succumbs.

Tumors may also be subclassified as follows: connective tissue tumors, muscle tissue tumors, epithelial tumors, endothelial tumors and pigmented tumors. A more detailed though not complete classification is shown in Table I.

TABLE I  
CLASSIFICATION OF TUMORS

<u>Tumor Type</u>	<u>Benign</u>	<u>Malignant</u>
I. Connective tissue	1. Fibroma (fibrous tissue) 2. Chondroma (cartilage) 3. Osteoma (bone) 4. Lipoma (fat)	1. Sarcoma (cellular)
II. Muscle	1. Myoma (smooth muscle)	-----
III. Epithelial	1. Papilloma (surface epithelium) 2. Adenoma (glandular epithelium)	1. Epithelioma (squamous cell) 2. Carcinoma (glandular epithelium)
IV. Endothelial	1. Hemangioma (blood vessels) 2. Lymphangioma (lymph vessels)	1. Endothelioma (endothelial cells)
V. Pigmented	1. Nevus (pigmented mole)	1. Melanoma

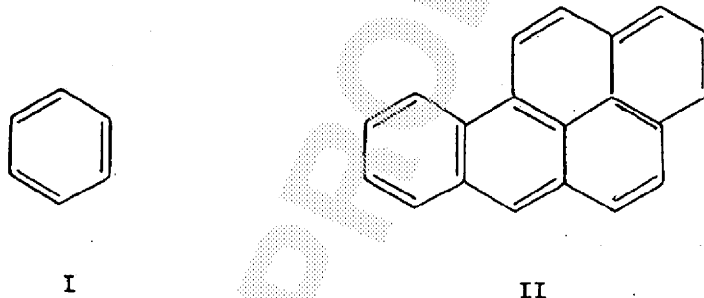
Spontaneous cancer is the rapid and unrestrained multiplication of an abnormal cell whose abnormality is caused by agent or agents unknown. Occupational cancer is the rapid and unrestrained multiplication of an abnormal cell whose abnormality resulted from prolonged or repeated exposure to known tars and oils, or certain metals, e.g., zinc, beryllium, arsenic, nickel. Experimental cancer results from the deliberate and often repeated application of a carcinogen (see

below) to laboratory animals for the purpose of studying the action of the particular carcinogen in question. In this manner, certain normal cells are presumably converted to abnormal ones and subsequent multiplication of this abnormal cell gives rise to a tumor. To date, very little has been learned about the mode of action whereby the carcinogen converts the normal to an abnormal cell.

A carcinogen is a substance or agent which, when administered to laboratory animals (or man), either orally, by skin painting, by injection (intravenously, subcutaneously, intraperitoneally), by implantation, by inhalation, or by irradiation, produces a tumor, i.e., cancer, under the conditions of the experiment in question. Thus, 3,4-benzpyrene is a carcinogen for the mouse by subcutaneous injection or skin painting since tumors will arise with a certain dosage after a certain latent period in this species. This substance is non-carcinogenic for the monkey under any circumstance since even after 12.5 years' exposure, tumors are not produced in this species.

A definition of the term aromatic polycyclic hydrocarbon follows: The term hydrocarbon refers to a compound comprised solely of the elements carbon and hydrogen. The term aromatic refers to the pleasant odor (in dilute concentration) possessed by certain of the simplest members of this type of compound. The simplest

aromatic hydrocarbon is benzene (I), a well-known commercial solvent. Notice that benzene possesses the so-called ring structure. Polycyclic refers to compounds containing two or more fused benzene-type rings, e.g., 3,4-benzpyrene (II).



Greene (1664) has very effectively described cancer as a disease which, unlike other diseases, does not require the continued activity of the inducing agent (or carcinogenic agent) and in this respect resembles an automobile engine which is dependent on the

self-starter for the original starting impulse, but once running, is completely independent of this mechanism. Thus, cancer is often spoken of as an autonomous or "independent" growth because its growth is unrestrained, independent of the continued activity of the inducing agent and, when fully evolved, is independent of the factors concerned in its development and origin.

This autonomous and independent feature of cancer is dramatically illustrated by the following quotation from the testimony of Dr. Clarence Cook Little (2082), chairman of the Scientific Advisory Board of the Tobacco Industry Research Committee, before the Blatnik Committee investigating false and misleading advertising in the matter of filter-tip cigarettes:

"Most people don't realize that an early cancer is a terrifically vigorous, virile, healthy biological unit, more healthy and more vigorous than the body in which it originates. That is why it 'outeats' it, outlasts it, and eventually kills it. If you remove a cancer from the body and culture it in a test tube, or if you transplant it from animal to animal, it is essentially immortal. There are mouse cancers alive today 30 years after they were discovered, and the Methuselah among mice isn't more than 3 years old.

Therefore, this original mouse tissue, this cancerous tissue, has lived 10 times as long as the oldest living mouse, yet it was a part of a mouse and is a part of a mouse."

Greene (2075-A) has given a simple but sound description of the cell structure of the human lung and of the cellular changes which have been recognized. He points out that human organs and tissues subjected to prolonged environmental contact are provided with a covering made up of cells of a special type, known as epidermoid cells, which cover the skin, the tongue, the lining of the mouth and nose and other such organs. Because of their structure and the number of layers in which they appear, they supply insulation and protection for the body. In contrast, the cells lining the tubules of the lung are of a different type -- being columnar or glandular in structure and not stratified in multiple layers. It is from such columnar or glandular cells that cancer of the lung arises. One of the most interesting facets of the etiology of lung cancer is the anomaly presented by the fact that cancer of the lung is an epidermoid carcinoma, similar in all respects to the carcinomas of the skin or mouth or lips.

Obviously, says Greene, before a glandular or columnar cell can produce an epidermoid carcinoma it has to undergo a change in cells. This change from a columnar to an epidermoid type of cell is known as metaplasia, which is not an uncommon finding in the body. Metaplasia, incidentally, is a general term encompassing the transformation of any tissue into another

type of tissue without the intervention of embryonal tissue. In subsequent sections of this memorandum, it will be noted that different investigators employ slightly different definitions of the term metaplasia. Indeed, pathologists are notorious for their inability to agree either on the classification of cellular lesions or on the interpretation of the meaning of these lesions.

A simple description of the human respiratory system and its physiological response to inhaled irritants, very useful as an introduction for the layman, was given by Dr. Norton Nelson at the National Conference on Air Pollution (held in Washington, D. C., November 18 - 20, 1958 under the auspices of the United States Public Health Service):

"The respiratory tract can be considered to be made up of the conducting airways from the nose through the pharynx and trachea and into the bronchi. These, after many successive branchings, lead into small terminal sacs, estimated to be some 50 million in number, called alveoli. It is in these tiny units that the end purpose of respiration is accomplished, the exchange of oxygen and carbon dioxide. With progressive branching of the respiratory tree, the diameter of the conducting airways decreases, reaching a final diameter of less than a millimeter. The exposed surface area increases enormously; the analogy often given is that the surface area of the alveoli is equivalent to that of a tennis court. The tissues making up these two major parts of the system, the conducting airways and the alveoli or deep lungs, are quite different in character. The con-



ducting airways have muscular tissue in them and can constrict; bronchial constriction, for example, is the source of the respiratory distress in asthma. The conducting airways are lined with a relatively tough layer of cells which bear cilia or small microscopic fingers which sweep inhaled foreign substances out of the lungs with a whip-like motion. The bronchial lining also contains glands which secrete mucus. The deeper parts of the lungs where gas exchange occurs do not have this protective layer of epithelium and in fact only a single very thin layer of cells lies between the very extensive bed of capillary blood vessels and the air spaces. One can readily see therefore that chemical irritants might well produce different consequences, depending on whether the irritant action occurs in the upper respiratory system, or in the deeper part, or in both. When a sufficient concentration of irritants contacts the upper airways coughing and respiratory distress shortly result. Other effects on the lining tissues of the bronchi include interference with the action of the cilia, the lung cleansing system, or change in the rate of secretion of mucus. Damage to the cilia and change in their rate of motion have been shown to result from exposure to sulfur dioxide and synthetic smog. Gases of high solubility may not penetrate beyond the conducting airways and so effects of the kind just described are all that might be seen.

However, when irritants succeed in passing beyond the bronchi and enter the alveoli, the consequences of irritant action are different. Here the primary immediate effects appear to be on cell permeability, or what may be called the 'leakage rate'. Generally, the effect is to lead to the passage of fluid into the alveolar spaces from the bloodstream. There also may be a change in the caliber of the capillary blood vessels of the lung in contact with this space. The entry of fluid into the air exchange units increases the distance through which oxygen and carbon dioxide must diffuse, and so impairs their exchange. There also is a reduction in the space available for gas in the lungs, and in extreme cases, whole sections of the lung

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2025018077

may be thrown out of effective use by being literally drowned with the fluid. It can be readily seen that these irritant gases in the deep lungs would make respiration more difficult and would put increased demands on the heart. It is through mechanisms such as these that irritant gases in gas warfare or intense accidental exposure cause severe symptoms or even death. The movement of fluid into the air spaces often require time to develop into a serious threat; accordingly there may be a delay of hours or even several days before the full effects become manifest.

Now, clearly the irritant gas or particle must reach these deep tissues for the described consequences to develop. Since the rather efficient scrubbing action of the upper airways may prevent highly soluble gases from reaching the deep lung, it is the group of irritant gases of moderate and low solubility that is of particular importance in producing irritation of the deep lungs. However, there is some evidence that the simultaneous presence of particles may aid in the transport of the more soluble gases into the deep lungs \* \* \*." (pp. 211-212)

GLOSSARY

Adenocarcinoma: adeno - relating to glands;  
carcinoma - cancer.

Alveolar: the ultimate division of bronchi  
emptying into the air space.

Anaplastic: restoring a lost or defective part; an  
agent that facilitates repair; (of tumors) having  
a high degree of malignancy.

Atelectasis: imperfect expansion or collapse of the  
air-vesicles of the lung.

Autopsy: a post-mortem examination to determine the  
cause of death; necropsy.

Benign: not malignant.

3,4-Benzpyrene: a carcinogenic hydrocarbon isolable  
from coal tar pitch; also found in cigarette  
smoke and auto exhaust.

Bilobectomy: the removal of both lobes of an organ,  
e.g., the lung.

Bronchi: two tubes into which the trachea divides  
opposite the third dorsal vertebra, called the  
right and left bronchus.

Bronchial secretions: matter secreted by the  
bronchi.

Bronchiectasis: a dilation of the walls of the  
bronchi; it may involve a tube uniformly, pro-

ducing the cylindrical type; or it may occur irregularly in sacs or pockets, producing the sacculated form; the characteristic symptom is paroxysmal coughing, with an expectoration of large quantities of mucopurulent, often fetid matter.

Bronchogenic carcinoma, bronchial carcinoma: cancer of the lung.

Bronchopulmonary: relating to both the bronchi and the lungs.

Bronchoscopy: examination of the interior of the bronchial tubes by the use of a bronchoscope.

Buccal mucosa: the mucosa or mucous membrane of the cheek and mouth.

Cancer: any malignant growth.

Cardiovascular: pertaining to the heart and blood vessels.

Carcinogenesis: the origin or production of cancer.

Chemotherapeutic: treatment based on the affinity supposed to exist between various chemicals and body tissues or invading microorganisms.

Cytologic examination: the examination of cell formation and cell life.

Diagnosis: the determination of the nature of a disease

Diaphragm: the wall, muscular at the circumference

and tendinous at the center, that separates the thorax and the abdomen.

Distillate: the product obtained by distillation.

Edema: an infiltration of serum into a part; a swell.

Endobronchial: within the bronchi.

Epidemiology: the science of epidemic diseases.

Epidermoid: a tumor formed of epidermoid cells (outer layer of cells) (see also squamous).

Epithelium: the term applied to the cells that form the epidermis, that line all canals having communication with the external air, and that are specialized for secretion in certain glands.

Etiology: the causation of a disease.

Excision: the cutting out of a part.

Extirpation: the complete removal of a part.

Extrapolation: projection by inference into an unexplored situation from observations in an explored field, on the assumption of continuity or correspondence, as from experiments with animals to man.

Fibrosis: development of fibrous tissue.

Hemoptysis: the spitting of blood from the larynx, trachea, bronchi or lungs.

Hyperkeratosis: hypertrophy of the horny layer of the skin.

Hyperplasia: an abnormal increase in the number of cells.

Hypertrophy: increase in size of tissue independent of the general growth of the body.

Intravascular: within the blood vessels.

Latent: concealed; not manifest; potential.

Laryngectomy: extirpation of the larynx.

Larynx: the organ of the voice, situated between the trachea and the base of the tongue.

Lesion: an injury, wound or morbid structural change.

Leukoplakia: the whitening of a surface, usually occurring on the gums, tongue or inner surfaces of the cheek.

Lobes: a more or less rounded part or projection of an organ, separated from neighboring parts by fissures and constructions.

Lymph: a nearly colorless coagulable fluid, contained in the lymphatic vessels, and consisting chiefly of blood plasma and colorless corpuscles.

Lymphatic: pertaining to the lymph.

Malignant: threatening life.

Mediastinum: the space left in the middle of the chest between the two pleurae (serous membrane enveloping the lungs) divided into the anterior, middle posterior and superior mediastinum.

Metaplasia: a transformation of a tissue into another

without the intervention of embryonal tissue.

Metastasis: the transfer of a diseased process from a primary focus to a distant focus by conveyance of causal agents through the blood vessels or lymph channels.

Morbidity: the quality of disease or of being diseased.

Mortality rate: the ratio of the number of dead individuals to the total population of a place usually calculated at a certain time or for a certain time.

Nodular: composed of or covered by knobs or protuberances.

Necropsy: the examination of a dead body; autopsy; post-mortem.

Oat-celled cancer: the cells when viewed under a microscope have the characteristic shape of an oat grain.

Palliative: relieving or alleviating suffering; a drug which relieves the symptoms of a disease without curing it.

Panacea: a cure-all or quack remedy.

Papilla: any small pimple-like projection or part.

Papilloma: a growth on the skin or mucous membrane resembling hypertrophied papillae, e.g., a corn



or a wart.

Pathology: the science that treats of the modifications of function and changes in structure caused by disease.

Pericardium: the closed membranous sac enveloping the heart.

Periphery: the circumstance or external surface.

Pharmacology: the science of the nature and properties of drugs.

Pharynx: the musculomembranous pouch situated back of the nose, mouth and larynx and extending from the base of the skull to a point opposite the sixth cervical vertebra, where it becomes continuous with the esophagus; it is lined by mucous membrane covered in its upper part with columnar ciliated epithelium; in its lower part it is covered with stratified epithelium.

Pneumonectomy: excision of a portion of the lung.

Primary: first in time or importance: with respect to cancer, primary refers to the site of origin.

Pulmonary: pertaining to or affecting the lungs.

Radioactivity: a property possessed by certain substances of spontaneously emitting radiations which are capable of penetrating materials

opaque to ordinary rays of light.

Resect: to cut out a piece of tissue or of an organ.

Roentgenography: x-ray procedure.

Sputum: the secretion ejected from the mouth in the form of spit; it consists of saliva and mucus from the nasal fossae and the fauces; in diseased conditions of the air passages or lungs it may be purulent, mucopurulent, fibrinous or bloody.

Squamous: of the shape of a scale; scaly (see also epidermoid).

Synergistic: an agent cooperating with another; two drugs are said to be synergistic when the action observed by simultaneous administration is greater than the sum of their actions when administered separately.

Tar: a liquid resin obtained by the destructive distillation of various species of wood or coal; also employed to describe the material collected when cigarette smoke is trapped and the volatile material removed by slight vacuum or evaporation.

Thoracic: pertaining to or situated in the chest or thorax.

Thoracotomy: incision of the thorax or chest wall.

Thorax: the chest.

Trachea: the windpipe.

Tumor: a swelling, mass of cells, tissues or organs resembling those normally present in the body but arranged atypically, growing at the expense of the host but serving no useful purpose therein.

For ready reference, the following table, adopted from Shimkin (1089), gives the frequency of spontaneous pulmonary tumors in various mouse strains:

<u>Strain</u>	<u>Pulmonary Tumors, Percent of Animals 12-18 months old</u>
A	70-90
Swiss	40-50
B alb C (c)	15-25
I	10-20
Y	10-20
C <sub>3</sub> H	5-15
dba	5
C57 leaden (L or M)	<1
C57B (black)	<1

### III. BIOGRAPHIES

Brief biographies of some of the more important American personalities involved in the respiratory cancer-tobacco smoking controversy will now be presented. The protagonists of the respiratory cancer-tobacco smoking theory include Auerbach, Cameron, Chang, Dorn, Hammond, Levin, Lilienfeld, Ochsner, Shimkin and Wynder, any one of whom may act as an expert witness for a plaintiff in a cancer case against members of the Tobacco Industry. The authorities with a more scientific approach to the problem, i.e., they do not necessarily discount this theory completely but feel that the theory is far from proved, include Berkson, Greene, Hueper, Kotin, Little, Macdonald and Rigdon.

III-1

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A. The Proponents of the Respiratory Cancer-Tobacco Smoking Theory

Auerbach, Oscar (born 1905; M.D. 1929)

Dr. Auerbach is a pathologist connected with the Veterans Administration Hospital in East Orange, New Jersey. He is a member of some half dozen scientific societies and has published some 75 articles, several of which deal with the changes in the bronchial epithelium in relation to smoking and lung cancer (870, 870-A, 1204-A, 2111, 2270).

Cameron, Charles S.

Dr. Cameron is the medical and scientific director of the American Cancer Society. He has written about 20 articles and a book, "The Truth About Cancer" (3399). Several of his articles, written for the lay press (897, 1327), have stressed the fact that many scientists accept the statistical association between cigarette smoking and lung cancer but that the cause-and-effect relationship of this association is not yet answered. In expressing the opinions of the American Cancer Society, Cameron stated (897):

"The American Cancer Society has resolved to support....research efforts to identify whatever cancer-inciting substances may be in tobacco and its product and to find means of eliminating them.... It does not hold that smoking causes cancer of the lung. It

IIIA-1

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does not propose to tell the public not to smoke. It does intend to equip the national conscience with the information by which it can make up its own mind fairly...."

Chang, Suk Chul (born ; M.D. ;  
Ph.D. 1956)

Dr. Chang is a Korean, possibly working on postdoctoral research. He has published about one-half dozen articles on the microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and nonsmokers (565, 900, 2068, 2158, 2486).

Dorn, Harold F. (born 1906; B.S. 1929;  
M.S. 1930; Ph.D. 1933)

Dr. Dorn is a statistician with the Public Health Service in Bethesda, Maryland. He is a member of a dozen or more scientific societies and has published about fifty articles. He specializes in the epidemiology of cancer and vital statistics. He has published several noteworthy articles on the relationship of lung cancer and other diseases with tobacco usage (104-A, 919-B, 2761, 3257) and on the increase in lung cancer incidence (919). He is the author of the most recent prospective statistical study on the relationship between cigarette smoking and lung cancer (2761).

IIIA-2

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Hammond, E. Cuyler (born 1912; B.S. 1935;  
Sc.D. 1930)

Dr. Hammond is a statistician, specializing in the study of the epidemiology of cancer. He is a member of six scientific societies and has published about 35 articles, of which approximately 25 are concerned with the tobacco smoking-health problem (153, 650, 650-A, 650-C, 650-D, 650-E, 740, 956, 956-A, 956-B, 956-C, 956-D, 1609, 1674, 1674-A, 1674-AA, 2244, 2534, 2534-A, 2534-B, 3132, 3132-A, 3270, 3409, 3446). Dr. Hammond is one of the most vigorous protagonists of the lung cancer-cigarette smoke theory and in 1954 advanced the suggestion that the American Cancer Society statistical smoking study demonstrated a cause-and-effect relationship (153). He and Dr. Horn have been responsible for the statistical manipulation of the data obtained through the American Cancer Society study (153, 2534-A, 2534-B).

Levin, Morton L. (born 1904; M.D. 1930;  
Dr.P.H. 1934)

Dr. Levin is an epidemiologist in the employ of the State Department of Health, in Albany, New York. He is a member of eight scientific societies and has published about forty articles, of which about one-quarter concerns the cancer-smoking question (258, 671, 994, 1249, 2574). He has been a prime mover in

the attempt to legislate against certain types of cigarette advertising in which it is implied that cigarette smoke is "good and healthful." Dr. Levin, with respect to this campaign against cigarettes, stated that cessation of smoking by all smokers in the U.S.A. would result in a reduction of 43 percent in the death rate from lung cancer.

Lilienfeld, Abraham M. (born 1920; A.B. 1941; A.M. 1949; M.D. 1944)

Dr. Lilienfeld is Chief, Department of Statistics and Epidemiology, Roswell Park Memorial Institute in Buffalo, N. Y. He specializes in epidemiology and biostatistics. He is a member of some half-dozen scientific societies and has published about 40 papers in the scientific literature. He is a co-author of a recent review (3409) on smoking and lung cancer and was a member of the Study Group on Smoking and Health (1319). He has also presented the results of a study on the association of smoking with bladder cancer in humans (1249) which indicated

"that a significantly larger proportion of men with urinary-bladder cancer smoked cigarettes than did other classes of patients chosen for comparison. This association was limited to those who gave a history of having smoked for 30 years or more....."

and

IIIA-4

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".....these data.....are highly suggestive of a cause-and-effect relationship between cigarette smoking and bladder cancer....."

Ochsner, Alton (born 1896; B.A. 1918; M.D. 1920)

Dr. Ochsner is a thoracic surgeon, president of the Ochsner Medical Foundation in New Orleans and Chairman of the Department of Surgery, School of Medicine, Tulane University. He has been president of the American College of Surgeons, American Cancer Society and American Association for Thoracic Surgery.

He has published some 350 articles of which a great number concern lung cancer, with specific reference to the hazards of cigarette smoking (308, 309, 695, 695-C, 695-D, 695-F, 696-D, 1037, 1038, 2341, 3173, 3173-A, etc.). He has also written a book for the lay public on the dangers of cigarette smoking (590).

He is one of the most vehement adherents to the lung cancer-cigarette smoking theory although he has not published or conducted any statistical or biological studies of the effect of cigarette smoke on a host, nor has he investigated chemically the composition of smoke.

Shimkin, Michael B. (born 1912; A.B. 1935; M.D. 1937)

Dr. Shimkin is Medical Director of the U. S.

Public Health Service at Bethesda, Maryland. He specializes in clinical and biological investigations on the etiologic factors in mammary and pulmonary tumors in mice. He has written about 150 articles, mostly dealing with experimental lung cancer, one of which is an excellent review article on this subject (1089). With respect to the lung cancer-smoking question he has co-authored several papers (954-A, 1156, 1219, 2792, 3130, 3409) which support the lung cancer-cigarette smoking hypothesis.

As to lung cancer induced in experimental animals, he has said (1089):

"Studies with tobacco fumes are somewhat more controversial. Lorenz *et al.* [268] failed to elicit pulmonary tumors in Strain A mice exposed to tobacco fumes. Essenberg [113], however, succeeded in demonstrating that cigarette fumes increased the number of such tumors in mice. Strain A mice were exposed to cigarette fumes for one year, and 21 out of 23 animals developed pulmonary tumors, as compared with a frequency of 59 percent among 32 unexposed controls. In this connection, the carcinogenic effect of the products of tobacco has been described by Roffo [349], who obtained carcinomas of the ears of rabbits painted with tars from tobacco, and by Flory [127], who obtained papillomas and two carcinomas in mice. The recent publication of Wynder *et al.* [475] summarizes the subject of experimental production of carcinoma in mice with cigarette tar, and reports the induction of epidermoid carcinomas in 44 percent of 81 mice painted with condensates obtained from cigarettes. The evidence seems convincing that under certain conditions tobacco fumes ..... may contain carcinogenic materials."

IIIA-6

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Wynder, Ernest L. (born 1922; B.A. 1945; B.S. 1950; M.D. 1950)

Dr. Wynder is Head, Section of Epidemiology at the Sloan-Kettering Institute, New York. He specializes in the study of the environmental factors involved in the development of human cancer. He has written approximately 50 articles of which about three-quarters are involved with the cancer-smoking controversy. His three areas of interest in research are as follows:

- (a) the relationship of cigarette smoke and lung cancer (472, 472-A, 473, 474, 475, 599, 600, 725, 725-A, 800-B, 1134-A, 1134-B, 1134-C, 1134-D, 1299-A, 1300, 1450, 1450-A, 1990, 2054-E, 2074, 2231, 2446-A, 2447, 2447-A, 2448, 2722, 2722-A, 2924, 3372, 3372-A, 3525, 3858) in which the publications concern statistical studies, animal experimentation and chemical analysis of smoke;
- (b) the relationship of cigarette smoke and alcohol to laryngeal and oral cancer (1135, 1135-A, 2054-B, 2054-D, 2100, 2446); and
- (c) the relationship of circumcision of the male to cancer of the cervix in the female sexual partner [Am. J. Obst. Gyn., 68, 1016-1052 (1954)]. Recent statistical results

IIIA-7

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presented by Dunn and Buell (3599)  
disagree with those presented by Wynder  
et al.

Wynder is a devout advocate of the smoking-  
cancer theory and recently outlined (3525) his feel-  
ings as to the validity of this theory as follows:

"The sum total of evidence linking smoking  
to cancer of the respiratory tract is based  
upon different types of evidence: pre-  
sumptive, epidemiological, pathological,  
animal and chemical. All of the evidence  
so far established demonstrates smoking to  
be a carcinogenic factor. It is now our task  
to bring the problem posed by this associa-  
tion to a successful solution...."

IIIA-8

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## B. The Opponents

### Berkson, Joseph

Dr. Berkson is head of the Section of Biometry and Medical Statistics at the Mayo Clinic. At one time he was a member of the Committee of Research and Statistics of the American Cancer Society, from which the project of Hammond and Horn (153, 2534-A, 2534-B) was launched, and under whose formal supervision the project was conducted.

He has published several articles (875, 1032, 2118, 2463, 2935, 3546) criticizing the conclusions drawn by Hammond and Horn from their statistical studies. Dr. Berkson's feelings on the cancer-smoking controversy are summed up in his own words (3546):

".... I felt very strongly that to announce definitely, on the basis of these statistical results (153, 2534-A, 2534-B), that smoking causes cancer of the lung, as many commentators did, was premature. For one thing, the question of the cause of cancer is basically a biologic, not a statistical problem, and the statistical conclusions would have to be fully corroborated by experimental and direct observational studies before they could be considered to have been scientifically established. There was, in fact, virtually no substantial clinical, pathologic, or other independent direct evidence that smoking was the cause of cancer of the lung ...."

Greene, Harry S. N. (born 1904; M.D. 1930)

Dr. Greene is Professor of Pathology and Chairman, Department of Pathology, Yale University

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School of Medicine, New Haven, Conn. His prime interest is cancer research with particular emphasis on tumor transplantation techniques. He is a member of some 15 scientific societies and is a member of the editorial board of the journals CANCER and CANCER RESEARCH.

He has published almost 100 articles of which several concern the lung-cancer smoking theory (1664, 2075-A). Dr. Greene has stated his views on this subject in the following language (1664):

"....the methods employed in the statistical inquiry under question, particularly the type of data used for analysis, raised doubts that the results obtained could be interpreted as conveying a suggestion of a causal relationship between tobacco smoking and lung cancer. However, the results were accepted by some investigators as sufficiently suggestive to warrant a directed experimental approach. The investigation has been reported as it progressed, and from my own point of view, has not succeeded in supplying confirmatory evidence.

"The evidence from both approaches, statistical and experimental, does not appear sufficiently significant to one to warrant forsaking the pleasure of smoking...."

Hueper, William C. (born 1894; M.D. 1920)

Dr. Hueper is Chief, Cancerogenic Research Laboratory at the National Cancer Institute, Public Health Service, Bethesda, Md. He specializes in the study of the environmental causes of cancer. He is a member of some 15 scientific societies and has

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published approximately 200 articles, over half of which concern lung cancer. He has published about a dozen or so articles in which he discusses the lung cancer-smoking theory (193, 199, 201, 970, 970-B, 970-D, 970-F, 657, 657-F, 1707-A, 1707-C, 3140, etc.).

Concluding a recent article, Hueper stated (1707-C):

"These observations, considerations, and interpretations of a large mass of factual and circumstantial evidence obtained from various sources and collected from different viewpoints do not favor the concept that the great majority of lung cancer, particularly those in men, are caused by excessive cigarette smoking. The epidemiologic evidence concerning this factor, on the other hand, is sufficiently impressive to attribute to cigarette smoke a definite, while less direct or indirect, role in the production and rise in frequency of cancer of the lung..."

This represents a modification of his earlier opinions.

Hueper also stated in this article (1707-C) that

".....This assessment of the probable role of cigarette smoking in the lung cancer problem, however, in no way weakens the fact that excessive cigarette smoking is an unhealthy habit.....and therefore should be discouraged."

Kotin, Paul

Dr. Kotin is Associate Professor of Pathology, University of Southern California School of Medicine and a member of the Scientific Advisory Board of the Tobacco Industry Research Committee.

With respect to lung cancer causation Kotin

(982) noted:

".....Of the two suggested major etiologic factors, cigarette smoking alone appears the least capable of adaptation to the panorama of lung cancer as it is currently manifest. The limitations of the tobacco concept of etiology are evident in studies showing differences in lung cancer rates on the basis of socioeconomic status. Geographic studies singling out urbanization as the exclusive variable in groups with contrasting lung cancer rates cast further doubt on the validity of the major roles assigned to tobacco in pulmonary cancer....."

and also

"....Any conceivable role of tobacco smoking in the pathogenesis of lung cancer appears to this reviewer to be at the level of a non-specific irritant or eluting agent for previously deposited carcinogenic agents. There is at present no convincing evidence that tobacco (smoke) possesses the necessary qualifications for the initiation and promotion of lung cancer."

Little, Clarence C.

Dr. Little is Director Emeritus of the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. He is Scientific Director of the Tobacco Industry Research Committee and Chairman of its Scientific Advisory Board. He has authored numerous articles, several of which concern the lung cancer-cigarette smoking theory (1000, 1250, 2082, 2304-A, 3159).

Dr. Little recently summarized (2082) his ideas on the smoking-cancer theory as follows:

"The statistical association reported between excessive cigarette smoking and lung

IIIB-4

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cancer have pointed out the need for greatly intensified research. They have not provided the answers - nor can any purely statistical association do so.

"Nonsmokers get lung cancer. The vast majority of heavy smokers never get lung cancer. Obviously, there is no simple cause and effect mechanism resulting from cigarette smoking."

Macdonald, Ian G. (born 1903; M.D. 1928)

Dr. Macdonald is Professor of Surgery at the University of Southern California School of Medicine. He is a member of the National Board of Directors of the American Cancer Society. He has written about 40 articles dealing with mammary, bone, uterine and lung cancer.

He has recently summarized his views concerning the lung cancer-cigarette smoke theory (2084):

"..... the total evidence .... fails to establish any sound basis on which a causative influence may be assigned to cigarette smoking in the production of cancer of the lung."

Rigdon, R. H. (M.D.)

Dr. Rigdon is Professor of Pathology, University of Texas Medical Branch, Galveston, Texas. He has published numerous articles on the incidence of lung cancer in relation to smoking habits, diagnosis, number of physicians and hospital beds, etc. (697, 698, 926, 1063, 1413, 1736, 1911, 1911-A, 1911-C, 1911-D, 1911-E, 1914, 3016, 3626), on carcinogenesis with 20-

IIIB-5

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methylcholanthrene (1275, 1275-A, 1275-B, 1412, 3347) and tobacco smoke condensate (3508-A), in addition to other articles on cancer (1411, 1911-B).

In 1957, Dr. Rigdon wrote (1911):

"The frequency of the habit of smoking by peoples throughout the world during the past several hundred years and the relative infrequency of cancer of the lung should make us critical of the observation suggesting an association between cigarette smoking and cancer of the lung as 'cause and effect.' Diseases other than lung cancer occur in individuals who are heavy smokers without anyone suggesting 'cause and effect.' Furthermore, many individuals have died with cancer of the lung that did not smoke....."

and (1911-A):

"In conclusion, it is my opinion that the data on which the relation of cigarette smoking to lung cancer is based are not sufficient to justify the conclusions which have been drawn by certain statisticians."

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#### IV TOBACCO SMOKING AND RESPIRATORY CANCER

##### A. EARLIEST CHARGES AGAINST TOBACCO

The early charges listed here are representative rather than all-inclusive, and are presented for the sake of perspective and in connection with the issue of notice to the defendants of the alleged harmful aspects of tobacco smoke. The reader will note that most, if not all, of the papers mentioned in this section, are either undocumented opinion or are based on inadequate samples. As mentioned earlier, the present expanded scope of the attack on cigarettes and smoking dates largely from the 1950 publication of Wynder and Graham (474), which probably created an impression because it was the earliest paper reporting such a relatively large number of subjects.

One of the earliest references to the claimed adverse effect of tobacco smoke on the lungs is contained in an epigram written by Samuel Rowlands around 1600:

"But this same poyson, steeped India weede,  
In head, hart, lunges, do the soote and copwebs breede  
With that he gasp'd, and breath'd out such a smoke  
That all the standers by were like to choke."

In 1880, Tillmans (1116) noted that tobacco smoking might be important as a cause of cancer of the respiratory tract.

In 1912, Adler (1451) in his monograph on primary malignant growths of the lung and bronchi suggested that tobacco smoking might be important in the development of bronchogenic carcinoma. This monograph is often quoted as the first reference to cigarette smoking as a cause of lung cancer but, in fact, only has a passing reference to the "abuse of tobacco and alcohol" as a reason why lung cancer incidence is higher in males than in females. Adler's monograph - a notable review in its day- comprised a total of 374 cases of cancer of the lung: These were the sum total of all lung cancer cases reported in the medical literature up to 1912.

In 1927, Tylecote (449), in a letter to the editor of LANCET, noted the following with respect to cancer of the lung:

"I have no statistics with regard to tobacco, but I think that in almost every case I have seen and known of the patient has been a regular smoker, generally of cigarettes."

Perret (328) in a study reported in 1927 of primary intra-thoracic malignancy stated that the great pandemic of influenza of 1918, the increased inhalation of irritating gases from automobiles, the dust from the roads and streets, imperfect fuel combustion, industrial processes, excessive smoking are probable

factors of importance. Eight cases are reported. Five of 6 for whom information is available used tobacco, 4 to excess.

In 1928, Lombard and Doering [NEW ENG.J. MED., 198, 485-487 (1928)] in a statistical study conducted in Massachusetts noted that heavy smoking was more common in the cancer group than among the controls. The controls were obtained by having the same investigator who collected the record of the cancer patient fill out a similar record for an individual without cancer, of the same sex and approximately the same age. In their sample, heavy smoking was largely pipe smoking and was particularly more common in those individuals with cancer of the buccal cavity.

Lickint (259) in 1929 wrote a lengthy review involving over 150 references on tobacco and tobacco smoke as an etiologic factor in carcinoma of the respiratory tract. The biological investigations of tobacco smoke of Brosch (52) in 1900, Stoeber (414) in 1910, Wacker and Schmincke (453-A, 453-B) in 1912, Hoffman et al. (180) in 1923 and Helwig (159) in 1928 were described. The results of these studies will be described in subsequent sections on the biological and chemical investigations of tobacco smoke.

IV-A-3

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In 1929, Hoffman (179) reviewed the literature on cancer of the lung with particular emphasis on increasing incidence and theories as to etiology. Regarding tobacco, he stated that there is no definite evidence that smoking habits are a direct contributory cause toward malignant growths in the lungs.

From 1930 to 1945, Roffo (344, 345, 346, 346-A, 348, 349, 350, 351, 353, 357, 361, 362, 363, 365, 367, 368, 370, 371-A) published the results of numerous biological studies on the carcinogenic effect of the distillate obtained from tobacco. Roffo maintained on the basis of these experiments and his clinical experience that over 90% of the cases of lung cancer in the human male were due to tobacco smoking.

Wynder et al. (475) subsequently discounted the biological results of Roffo and many of the other early investigators because the tobacco smoke condensate or distillate was not produced under conditions simulating the human smoking habit. Roffo's experiments involved the destructive distillation of the tobacco, collection of the distillate at various distillation temperatures and applications of the distillates and still residue to the ears of the rabbit by painting. A fairly high percentage of the animals developed tumors on the area of the ear treated with the still residue. The nicotine fraction showed no carcinogenic activity (349)

Incidentally, Roffo was one of the first to claim that polluted air was implicated in lung cancer; that heated fats were a factor in stomach cancer; and that roasted coffee was carcinogenic. In short, he was an early worker in the cancer field, who espoused a number of postulates still popular today.

The first suggestion that tobacco contained precursors to the polycyclic hydrocarbons, i.e., compounds which at high temperature yield polycyclic hydrocarbons, many of which are carcinogenic, was advanced by Roffo (371). Extraction of tobacco to remove the phytosterols, etc. followed by destructive distillation of the extracted tobacco gave tars with very low carcinogenic activity compared with those from the non-extracted control tobacco. The biological and chemical studies conducted by Roffo will be discussed in detail in a subsequent section of this report.

In 1931, Hoffman (181) published a paper in which he accused tobacco of being a cause of cancer of the respiratory tract. He included in his series of cancer cases 27 with cancer of the lungs. Of these, 67% were heavy smokers compared to an incidence of 42.3% among a series of 537 non-cancer males. He summarized his publication with the following comments:

"Smoking habits unquestionably increase the liability to cancer of the mouth, the throat, the esophagus, the larynx and the lungs.... The increase in cancer of the lungs observed in this and many other countries, is, in all probability, to a certain extent directly traceable to the more common practice of cigarette smoking and the inhalation of cigarette smoke. The latter practice unquestionably increases the danger of cancer development."

Hoffman did note, however, that factors other than cigarette smoke must also be involved.

In 1932, McNally (277) wrote an article on the tar in cigarette smoke and its possible effects in which he concluded:

"The tar of cigarette smoke...could account for 'cigarette cough' the chronic bronchitis of the cigarette smokers, the leukoplakia in heavy smokers, and the recorded increase of cancer of the lung."

Brockbank (57) reported in 1932 a series of 52 male and 10 female patients with lung cancer of which 21% never smoked and 14.5% smoked excessively. He concluded that poison war gas, tobacco smoking, road dust, and motor car fumes are all possible etiologic factors.

Boycott (42) stated in 1932 that environment as a whole has become less carcinogenic; there is more soap and hot water, less irritating food, the air is cleaner, the general standard of life has greatly improved. On the other hand, he noted that we have much more tobacco, and, more recently, petrol engines and tarred roads; he concluded that whatever the agent, it



produces lung cancer much more frequently in men than in women.

Hruby and Sweany (187) analyzed a large number of case histories of primary cancer of the lung and found a tremendous and unquestioned increase in its incidence. They stated in 1933 that while disease, smoke, dust and modes of living may have been the cause of some of the increase, better diagnosis and changed conditions have contributed the most. In an editorial entitled "Cancer of the Lung" [J.A.M.A. 108 (2), 1716-1717 (1937)] comment was made on the increased incidence of cancer of the lung and it was mentioned that, among the contributing factors to this increase, the injurious effects of tobacco smoking, exhaust gases from automobiles, tar on roads and the influenza epidemic of 1918-1919 had been suggested. None of these were accepted as causative.

In 1936, Arkin and Wagner (14) published a study involving 135 cases (125 male; 10 female) of cancer of the lung and noted that 90% of the patients were chronic smokers. The authors stated that they believed the inhalation of tobacco smoke might be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi.

In 1936, Fleckseder (126) presented a report on 62 cases (53 male; 9 female) of cancer of the lung ob-

served by him over a 13-year period. Of the males, 68.8% were heavy smokers; altogether 94.4% were smokers. Fleckseder expressed the opinion that tobacco smoke irritates directly the bronchial mucous membranes resulting in cancer development.

The earliest controlled statistical study (other than that by Lombard and Doering, mentioned above, involving only 5 cases of lung cancer) by Muller (296), was published in 1939. This and the succeeding statistical studies will not be described here, but will be treated in a subsequent section on statistical studies.

In a bulletin published by the Metropolitan Life Insurance Co. entitled "Cancer of the Lung - A Growing Health Problem" [Statistical Bull. - Metropolitan Life Insurance Co. 20(11), 7-9 (1939)], it was noted that the more frequent recognition and reporting of the cause of death was probably responsible in large part for the increase in recorded mortality from cancer of the lung and pleura. Regarding smoking, it was stated that the habit since 1917 has become relatively more prevalent among women than among men. If smoking were of appreciable etiological significance, we might expect the death rate for the disease to increase more rapidly among women than among men. The reverse has actually

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been the case. It appeared doubtful to the author that smoking is a factor of etiological importance in cancer of the lung.

Ochsner and DeBakey (1859-J) presented an analysis of 79 collected cases and 7 personal cases of primary pulmonary malignancy. Concerning the increased incidence of the condition, they wrote, in 1939, that in their opinion the increase in smoking with the universal custom of inhaling is probably a responsible factor, as the inhaled smoke, constantly repeated over a long period of time, undoubtedly is a source of chronic irritation to the bronchial mucosa. They did not state whether or not their 7 patients were smokers.

Tripoli and Holland (435) analyzed 195 cases of primary carcinoma of the lung in 1940. Carcinoma of the lung was found to represent 10% of all malignant tumors, improved diagnostic methods having resulted in a marked increase in the frequency of recognition. The etiology was held to be unknown. They stated that the widespread incidence of influenza, and the equally general use of tobacco, suggest a possible relationship, but the association was not clear, and neither these nor any other factors could be demonstrated as causal in any of the cases in this series.

IV-A-9

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In 1940, Hammond (152) reported on 40 cases of carcinoma of the lung, the ratio being 4 males for each female. No information was given concerning the smoking habits of these patients. The higher rate in the male sex was attributed to excessive use of tobacco, the tar from the combustion acting as the carcinogenic agent. It was said that other irritating elements, such as chemical, mechanical, bacterial, thermal and radio-active agents, might also contribute.

DeBakey and Ochsner (94) expressed in 1940 their conviction of a significant relationship between the increased incidence of cancer of the lung in the United States and the increased production of tobacco.

In 1941, Menne and Anderson (282) reported 84 cases of bronchogenic carcinoma. With respect to etiology the authors claimed that the disparity in incidence of this disease in the sexes was attributable to either of the following: greater exposure of the males to occupational or industrial irritants or the significantly greater consumption of tobacco by males. They urged more careful recording of the histories as to how much particular persons smoke since the average inquiry simply elicited information that the patient was or was not a user of tobacco. It was felt that it was too early to observe in the statistics of the literature the possible influence that tobacco smoking might

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exert on the incidence of bronchogenic carcinoma in women, who were smoking cigarettes, often more excessively than men. Their reported series gave no data on the tobacco smoking habits of the patients.

Halpert [J.A.M.A. 117, 2221-2222 (1941)], in discussing Menne and Anderson's paper, stated that chronic irritation from infection, inhalation of gases, foreign bodies and particularly smoking of tobacco with its nicotine and tar content may play a part, but perhaps more important is the fact that more people are reaching the cancer age.

Ochsner and DeBaakey (311-A) stated in 1941 that every one of their patients with carcinoma of the lung, excepting 2 women, was an excessive smoker. They presented a graph showing a comparison of the death rate per 100,000 of population from cancer of the lung with the production of tobacco and automobiles in the United States during the 17-year period 1920-1936. The authors concluded that whereas there is no significant relation between the production of automobiles and cancer of the lung, there was an obvious parallelism between the increased production of tobacco and carcinoma of the lung.

It should be pointed out that, other than his own clinical observations on lung cancer in smoking, Ochsner has not conducted any controlled statistical study

biological study or chemical study in support of his contentions.

Roegholt (1065-B) is one of several authors who have disagreed with Ochsner's "parallelism theory" and he has noted that such commodities as automobiles have increased similarly to cigarette consumption. See subsequent discussion of Roegholt in the section of this paper on environmental factors in respiratory cancer causation.

Ochsner and DeBakey (1859-H) again expressed their conviction in 1941 that there is a significant relationship between the increased incidence of carcinoma of the lung in the United States and the increased production of tobacco.

In 1942 Macklin (279) critically reviewed the question of whether a real increase in lung cancer has been proved. Some of the fallacies in the statement that lung cancer is increasing far faster than cancer in general has increased, because it forms an increasingly large percentage of total cancer autopsies, were pointed out. Methods were suggested to eliminate the most obvious sources of error and it was recommended that those who have large autopsy records of cancer in general and of lung cancer re-examine their material using these methods. Macklin concluded that the data which were used to support

the idea that lung cancer has increased faster than other forms of cancer cannot be used to support that conclusion, since we do not know what proportion of lung cancer cases were unrecognized formerly and what proportion are unidentified today. We can merely state that diagnosed lung cancer is increasing at a rate which appears to be faster than that of other diagnosed cancers. Macklin further stated that the search for environmental factors supposed to be the basis of the unduly great increase in lung cancer should await further proof that the increase in diagnosed cases has been as spectacular as it has been claimed to be.

Wallace and Jackson (455) wrote in 1943 that tobacco plays a definite role in the causation of primary lung carcinoma. In this connection, they pointed to an increase in incidence of bronchogenic carcinoma in women in the past several decades and related this to the increased incidence of smoking in women during this period. They stated that it was entirely possible that the use of arsenic in curing tobacco and the arsenic content of tobacco smoke may substantiate the evidence from Schneeberg, and that the arsenic may well be the external irritant which is primarily responsible.

IV-A-13

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In 1943, Grace (140) stated that he had been impressed, during an experience of 10 years with a large series of patients with cancer of the lung, by two distinct elements: (1) the patients were almost always men and (2) they were heavy smokers. He presented 3 cases to illustrate the point and concluded that it would seem logical to assume that possibly in some biologically susceptible individuals, a carcinogenic agent in the tar of smoking tobacco might be the causative factor. He repeated this position in essence in "The Toxicity of Combustion Gases with Special Reference to Tobacco Smoke as a Carcinogenic Factor" Med. Times 72: 322-334, 1944.

In 1946, Ochsner [Life and Health, 625, 6-7, 34 (1946)] again stated that whereas undoubtedly smoking was not the only cause of lung cancer, it was the most important, and were it not for the constant and continued irritation from prolonged smoking, cancer of the lung would develop in relatively few cases.

An editorial entitled "Arsenic in Tobacco Smoke" (Brit. Med. J., 1946(1) 94) reviewed studies on the presence of arsenic in tobacco smoke and stated that in view of the high incidence of pulmonary carcinoma in arsenic workers, and with tobacco smoke known to contain arsenic, it was felt that here was a case worthy of full investigation.



In 1947, Ochsner et al. (311-B), on the basis of a total experience of 412 cases (356 males and 56 females) of primary cancer of the lung, reversed their earlier position and stated that both occupation and smoking, which had been particularly emphasized by some observers as possible etiologic factors, and which they were inclined previously to consider more seriously, were found to have no special significance in this analysis. Of 147 patients in whom pulmonary resection was performed 76% were smokers and 24% were non-smokers, and the number of those who had indoor occupations was almost equal to that of those who did outdoor work.

The reversal of position by Ochsner, just mentioned, prompts us to review briefly the history of the various positions he has taken in the smoking controversy. In a paper published in 1952 (1859-N), he wrote:

"There is a distinct parallelism between the sale of cigarettes and the incidence of bronchogenic carcinoma. . . . Because the carcinogenic effect of cigarette smoking does not become evident until after many years of smoking (approximately 20), it is frightening to speculate on the possible number of bronchogenic cancers that may develop as the result of the tremendous number of cigarettes consumed in the two decades from 1930 to 1950. . . . if there is a causal relationship between cigarette smoking and bronchogenic carcinoma the deaths per 100,000 population from this cause may be expected to increase from 11.3 to 29.4 by 1970."

On the other hand, he said in 1947 in the paper described in the preceding paragraph of this memorandum:

IV-A-15

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"In the analysis of this series none of these factors was found to bear a significant relation to the occurrence of the disease. Both occupation and smoking, which have been particularly emphasized by some observers as possible etiologic factors, and which we were inclined previously to consider more seriously, were found to have no special significance in this analysis."

The next year, Ochsner, et al. [POSTGRAD. MED., 3, 427-440 (1948)], reaffirmed this stand in connection with a series involving 489 cases of lung cancer. On several other occasions in 1947 and 1948, Ochsner, et al. reported:

".... In the 129 resected cases no factor was found which might bear a significant relationship to the occurrence of the disease. Neither occupation nor smoking habits, which some reports, including our own, have stressed of possible etiologic significance, seemed of any special significance in this particular series...."  
(311-A)

".... Although we have been unable to demonstrate that there is any causal relationship between smoking and primary bronchogenic carcinoma, the fact that the two have increased concomitantly and that smoking does produce a chronic irritation of the bronchial mucosa suggests that there might be some causal relationship between the two. In our series (Ed: consisting of 192 cases) we have not been able to show that there has been a higher incidence of smokers than in the average population as a whole." [CHICAGO MED. SOC. BULL., 51, 127-134 (1948)].

and

".... no etiologic factor has been found to have special significance" (1859-L)

The latter quotation concerns a series of 548 patients

observed by the authors from 1934 to 1948 in various New Orleans' hospitals.

Thus, after waxing eloquent on his "parallelism theory", Ochsner could provide no confirmatory data from his own clinical observations on many hundreds of lung cancer cases. However, he immediately rejoined the bandwagon when Wynder and Graham published the results of their retrospective statistical study (474) in 1950.

Mandell, in discussing the incidence of bronchogenic carcinoma of the lung, in 1947 made the following statements: Many types of lung irritants have been suspected and studied. These may be grouped as mechanical, such as trauma; chemical, as specific dusts and fumes; infections, such as tuberculosis, influenza, common cold, abscess and bronchiectasis; radioactive and thermal. While all of these may be suspected, none can be indicted and convicted. Since pipe-smokers often are victims of carcinoma of the lip, it was thought that a case was made against tobacco, as the disease was noted more frequently in men. However, of recent years women have been smoking at least as much as men and no increase in the incidence of bronchogenic carcinoma in women is yet apparent. The role of bronchial irritation cannot be taken too seriously. It is to be remembered that in a modern community we are

all constantly bombarded with coal dust and car fumes, but with the exception of the Schneeberg miners, no segment of the population seems more prone to the disease than another. There is no significant statistical difference in incidence between rural and urban population, between the north, south, east or west. It is to be remembered that perhaps the most common pathologic finding at autopsies is chronic inflammatory involvement of the bronchial and mediastinal lymph glands. So that apparently our bronchial tree is constantly invaded with bacterial and virus irritants. Unless a specific agent is necessary, irritation is too common and constant to be blamed too severely. One factor may be of importance, although proof is not yet at hand: a predisposition or special susceptibility, or a lack of a resistance factor may account for the occurrence of the condition in one and not in another. Yet this special condition of the host must be one which is acquired or lost, else it would be hard to explain why so many can go for so long without acquiring disease.

Bradshaw [North Carolina Med. J. 9, 186-189 (1948)] felt that there was no foundation on either experimental or clinical evidence that the difference in sex incidence of primary cancer of the lung is due to the smoking habits of the male. The incidence of

cancer in patients with truly irritating diseases of the bronchial tubes, such as bronchiectasis, had never been shown to be greater than in normal individuals. In addition, many patients, both male and female, who have lung cancers have never smoked.

Hayden [Med. Times, 76, 539-546 (1948)], discussing the early diagnosis of bronchogenic carcinoma, stated that like cancer elsewhere in the body, there was no proved carcinogenic agent known. Although tobacco smoking, particularly cigarette smoking, inhalation of gasoline and tar derivatives, inhalation of noxious gases and fumes incident to various occupations have been indicted in many reviews of this subject, there was no experimental proof that any of these was a factor in the pathogenesis of cancer.

IV-A-19

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B. STATISTICAL STUDIES

It had been suggested in 1912 by Adler (1451) that tobacco smoking might be important in the development of bronchogenic carcinoma. Numerous authors have referred to Adler (1451), who said:

"It has always been maintained that males are by far more frequently subject to lung tumors than females....The domestic life led by women, with their consequent retirement and immunity from the irritations and traumatisms which must be frequent in the more unprotected life of men (the abuse of tobacco and alcohol, the many trades and vocations which are accompanied by irritations of the respiratory organs, etc.) has been adduced in explanation of this fact. The entire subject is not yet ready for final judgment." (1451, p. 22)

and:

".....bronchial carcinomata are nearly always found in those places which are most subjected to slight, but chronic irritations,....Naturally, all the irritations of aspiration, of dust, tobacco and so on, as well as coughs, are apt to center about these points....." (1451, p. 36)

A clinical study to this effect was made in 1939 by Muller (296), and subsequently other investigators have conducted similar studies; but these studies involved relatively few individuals. None of the earlier investigations attracted the attention created by the publication in 1950 of Wynder and Graham's (474) report concerning the

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study of the smoking habits of 684 proven cases of lung cancer and the comparison of these cases with a comparable set of controls. Periodically since 1950 there have been published similar statistical studies purporting to show an association between cigarette smoking and lung cancer. The tobacco theory has reached its present vigor largely on the basis of (a) the Wynder and Graham paper in 1950; (b) subsequent statistical studies; and (c) papers reporting the carcinogenic activity of tobacco smoke condensate when painted on the backs of certain strains of mice. This section of this commentary will discuss the more important statistical studies seriatim and close with a summary of the case against cigarettes based on them, and a statement of the weaknesses that have been pointed out in the studies by those investigators skeptical of a cause-and-effect relationship between smoking and lung cancer.

IV-B-2

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# 1. TYPES; CHARACTERISTICS

Two types of statistical studies have been conducted in the past. These are the retrospective and prospective studies. Statistical studies of the retrospective type have been presented by some twenty-odd independent groups of investigators in eight different countries. In these studies persons with cancer of the lung, or their relatives, were questioned about the smoking history and other past events, and the answers compared with those of individuals without lung cancer who were selected as controls. Although the twenty-odd studies have certain features in common, they varied greatly in the methods of selecting the groups, the methods of interview, and other important aspects.

The association between smoking and cancer of the lung was further investigated in two countries by three independent groups [Hammond and Horn (153, 2534-A, 2534-B), and Dorn (2761) in the United States and Doll and Hill (628-B, 918-D) in England], using the so-called prospective method. In these studies, very large groups of persons were questioned about their smoking habits and some other characteristics, and the groups were observed for several years for data on mortality and causes of death. The three

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prospective studies also varied in several important details including the type of subjects, the selection of subjects, and the method of obtaining information on smoking habits.

In each of these studies, an association was found between cigarette smoking and cancer of the lung. In every investigation where the type of smoking was considered, a higher degree of association was found between cancer of the lung and cigarette smoking than between cancer of the lung and pipe or cigar smoking. In every instance where amount of smoking was considered, it was found that the degree of association with cancer of the lung increased as the amount of smoking increased. When ex-cigarette smokers were compared with current cigarette smokers, it was found that lung-cancer death rates were higher among current cigarette smokers than among ex-cigarette smokers.

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IV-B-4

## 2. INDIVIDUAL STUDIES

### a. Retrospective

In 1939, Muller (296) reported (in German) the results of a study conducted in Cologne on the relationship between cigarette smoking and cancer of the lung. From information regarding tobacco smoking, supplied by the patients themselves, or by members of their families, as well as from knowledge based on post-mortem findings, Muller found the following in his study of 86 cases of lung carcinoma: (a) excessive smokers in 29.07 percent of cases, (b) very heavy smokers in 20.93 percent of cases, (c) heavy smokers in 15.12 percent of the cases, (d) moderate smokers in 31.39 percent of cases. Patients with proved carcinoma of the lungs, who were nonsmokers, comprised 3.5 percent of the cases.

Excessively heavy smokers were defined in this study as those who smoked from 10-15 cigars per day or over 35 cigarettes or over 50 grams of pipe tobacco; very heavy smokers were defined as those smoking 7-9 cigars or from 25-35 cigarettes or 36-50 grams of pipe tobacco; heavy smokers were defined as those smoking 4-6 cigars or from 16-25 cigarettes, or 21-35 grams of pipe tobacco; and moderate smokers were defined as those smoking 1-3 cigars, up to 15 cigarettes,

or up to 20 grams of pipe tobacco per day. In the cancer cases studied by Muller, the total amount of tobacco smoked was 2.9 grams per day, while in the control cases the amount was only 1.25 grams per day. Muller concluded that tobacco smoking represented an important factor determining the onset of primary carcinoma of the lung and that the enormous spread of smoking is the real cause of the increase in frequency of this disease. See Tables II, III and IV for a summary of Muller's work. Table II is taken from a publication of Doll (918-B); Tables III and IV are taken from a publication of Cutler (777).

In 1943, Schairer and Schoninger (1078) conducted a similar study in Jena. This study also involved relatively few cases; 93 males with cancer of the lung, 270 control cases. The data presented by these authors confirmed the findings of Muller (296). See Tables II, III and IV for a summary.

In 1945, Potter and Tully [AM. J. PUBLIC HEALTH, 35, 485-490 (1945)] did note in their statistical study of cancer in Massachusetts that there was a definite association between cancer of the buccal cavity and the use of tobacco and that there appeared to be some association between the use of tobacco and cancer of the

TABLE II

**Principal Characteristics of Smoking Histories of Men  
With and Without Lung Cancer, Reported by Various Authors (918-B)**

Author	Date	Number of Men		Percentage of "Non-smokers"		Percentage of "Heavy Smokers"	
		With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer
Muller	1939	86	86	3.5	16.3	65	36
Schairer and Schoniger	1943	93	270	3.2	15.9	52	27
Wassink	1948	134	100	4.5	19.0	55	19
Schrek <i>et al.</i>	1950	82	522	14.6	23.9	18	9
Mills and Porter	1950	444	430	7	31	--	--
Levin <i>et al.</i>	1950	238	481	15.3	21.7	--	--
Wynder and Graham	1950	605	780	1.3	14.6	51	19
McConnell <i>et al.</i>	1952	93	186	5.4	6.5	35	22
Doll and Hill	1952	1357	1357	0.5	4.5	25	13
Sadowsky <i>et al.</i>	1953	477	615	3.8	13.2	--	--
Wynder and Cornfield	1953	63	133	4.1	20.6	68	29
Koulumies	1953	812	300	0.6	18.0	66	31
Lickint	1953	224	1000	1.8	16.0	74	29
Breslow <i>et al.</i>	1954	518	518	3.7	10.8	74	42
Watson and Conte	1954	265	277	1.9	9.7	73	57
Gsell	1954	135	135	0.7	16.7	86	33
Randig	1954	415	381	1.2	5.8	34	18

**Note:** It has not been possible to make all the figures in this Table completely comparable. Some series include, for example, a few women; in others the proportions of heavy smokers are based on totals which are different from those used to calculate the proportion of non-smokers. One series excludes adenocarcinoma. The individual papers should be referred to before any detailed use is made of the figures.

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TABLE III  
Description of 14 Retrospective Studies of Smoking Habits (777)

Study Reported By	Country	Year Reported	Lung Cancer Cases		Controls		Method of Collecting Data
			No.	Description	No.	Description	
Mueller (286)	Ger.	1939	86	Hospitalized lung cancer patients in Cologne, 1928-39.	86	Sample of men in general population falling within same age group as the patients.	Questionnaire to relatives of cancer patients. Methods used for controls not stated.
		1943	93	Deaths due to lung cancer in Thuringen, 1930-41. Average age was 53.9.	270	Sample of men in general population of same area; aged 53-54.	Questionnaire to relatives of cancer cases and to sample of men in general population.
Schaller & Schoniger (1078)	Ger.	1948	136	Hospitalized lung cancer patients	100	Sample of men in general population, in same occupational and age classes.	Interview. Diagnosis known.
Wassink (436-A)	Neth.	1950	82	Lung cancer patients seen in V.A. hospital in Illinois 1942-44.	552	Patients with cancer other than of lip, tongue, mouth, larynx, pharynx, esophagus, stomach, and lung admitted during same period.	Interview. Diagnosis known.
Schrek et al. (388)	U.S.	1950	444	Deaths due to respiratory cancer in Cincinnati, O., 1940-45 and in Detroit, Mich., 1942-46.	430	0.9% sample of white males, 20 years old or over, in Columbus, O. in 1947. Adjustment made for difference in age distributions of cases and controls.	Mail questionnaire to next of kin of cancer cases. Interviewed controls.
Mills & Porter (287)	U.S.	1950	605	Hospitalized lung cancer cases in different parts of the United States.	780	Admissions to general medical and surgical service in St. Louis hospitals. Adjustment made for difference in age distributions of cases and controls.	Interview. Diagnosis known, except for 100 lung cancer cases in a series of 286 admissions with variety of chest ailments.
Wynder & Graham (474)	U.S.	1952	93	Hospitalized lung cancer cases in Liverpool area seen 1946-49.	186	Hospitalized patients without cancer seen in same hospitals 1948-50.	Interview. Diagnosis known.
McConnell et al. (274)	Eng.	1952	1357	Hospitalized cases of lung cancer in various parts of England, 1948-51.	1357	Hospitalized patients without cancer matched for sex, age, hospital and admission date.	Interview. Diagnosis known, but in more than 200 cases initial diagnosis of lung cancer was found to be incorrect.
Doll & Hill (102, 103)	Eng.	1952	1357	Hospitalized cases of lung cancer in various parts of England, 1948-51.	1357	Hospitalized patients without cancer matched for sex, age, hospital and admission date.	Interview. Diagnosis known, but in more than 200 cases initial diagnosis of lung cancer was found to be incorrect.

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TABLE III (Cont'd)

## Description of 14 Retrospective Studies of Smoking Habits (777)

Study Reported By	Country	Year Reported	Lung Cancer Cases		Controls		Method of Collecting Data
			No.	Description	No.	Description	
Wynder & Cornfield (473)	U.S.	1953	63	Physicians who died of lung cancer 1949-52	133	Physicians who died of other forms of cancer, 1950-52.	Mail questionnaire to next of kin. Diagnosis known.
Sadowsky et al. (378)	U.S.	1953	477	Hospitalized cases of lung cancer in different parts of the United States, seen 1938-43.	615	Patients without cancer seen in same hospitals during same period. Adjustment made for difference in age distributions of cases and controls.	Interview - smoking data included with histories on a variety of subjects. Diagnosis known
Kouluomies (238)	Fin.	1953	712	Cases examined at a radiotherapy institute during 16-year period, found to have lung cancer.	300	Admissions to outpatient department in 1952 - men 40 years old or over; no cancer suspected.	Interview at time of admission.
Breslow et al. (615-A)	U.S.	1954	518	Hospitalized cases of lung cancer seen 1949-52 in various parts of California.	518	Admissions to same hospitals - matched for sex, age and race; without cancer or chest ailment.	Interview - Diagnosis known.
Levin (258, 631)	U.S.	1954	490	Admissions from 1938 on to State cancer hospital in New York; found to have lung cancer.	2365	Admissions during same period; found not to have cancer. Adjustment made for difference in age distributions of cases and controls.	Interview - smoking data part of regular case history upon admission.
Watson & Conte (460, 719-A)	U.S.	1954	265	Admissions 1950-52 to a thoracic clinic in New York City; found to have lung cancer.	267	Admissions to same clinic, found not to have lung cancer.	Interview at time of admission.

Note: These studies deal almost exclusively with white males.

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TABLE IV

SUMMARY OF FINDINGS REPORTED IN 14 RETROSPECTIVE  
STUDIES OF SMOKING HABITS (777)

Study Reported By:	Percent non-smokers		Percent heavy Smokers		Relative risk of developing lung cancer: Ratio to non-smokers	
	Lung Cancer		Lung Cancer		All Smokers	Heavy Smokers
	Cases	Controls	Cases	Controls		
Muller	3.5	16.3	50.0	10.5	5.4	22.2
Schairer & Schoniger <sup>1</sup>	3.2	15.9	31.2	9.3	5.7	16.7
Wassink <sup>2</sup>	5.0	19.0	55.0	19.0	4.5	11.0
Schrek, <i>et al.</i> <sup>3</sup>	14.6	23.9	18.3	9.2	1.8	3.3
Mills & Porter	7.0	31.0	--	--	6.0	--
Wynder & Graham	1.3	14.6	51.2	19.1	13.0	30.1
McConnel, <i>et al.</i>	5.4	6.5	38.5	23.8	1.2	1.9
Doll & Hill	0.5	4.5	25.0	13.4	9.0	16.8
Wynder & Cornfield	4.1	20.6	67.6	29.3	6.1	11.6
Sadowsky, <i>et al.</i> <sup>4</sup>	3.8	13.2	46.8	30.7	3.8	5.3
Koulumies	0.6	18.0	65.8	25.0	36.4	79.0
Breslow, <i>et al.</i>	3.7	10.8	75.6	44.2	3.2	5.0
Levin <sup>5</sup>	8.0	26.9	54.8	28.8	4.2	6.4
Watson & Conte	1.9	9.7	73.0	57.0	5.5	6.5

Note: Relative risk was computed by means of a technique developed by Cornfield.

Heavy smokers are defined here as persons smoking more than one pack of cigarettes per day, or its equivalent. Approximated from variety of smoking classes, with lower limits ranging from 20 to 26 cigarettes per day.

<sup>1</sup>Also compared cases with cancers of the tongue, esophagus, stomach, color and prostate with the same controls. The stomach cancer cases (numbering 128) were found to resemble the controls very closely. The cases with all other forms of cancer combined (numbering 98) had fewer non-smokers and more heavy smokers than the controls, but the difference was less striking than for the lung cancer cases.

<sup>2</sup>Numerical values of results approximated from graphic presentation.

<sup>3</sup>Also compared cases with cancers of lip, tongue, mouth, larynx and pharynx, esophagus, and stomach to same series of controls. Found no significant differences except for lip and for larynx and pharynx combined.

<sup>4</sup>Also compared cases with cancers of lip, tongue, mouth, pharynx, larynx, esophagus, and skin to same series of controls. Found positive associations between laryngeal cancer and cigarette smoking and between lip cancer and pipe smoking. Found a negative association between smoking and skin cancer.

<sup>5</sup>Also compared cases with cancers of lip, pharynx, esophagus, colon, and rectum to same series of controls. Found no significant differences except for lip.

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respiratory tract. This study involved only cancer patients reported in Massachusetts for a 3-year period in the early 1940's; no control population was used.

In 1948, Wassink (456-A) published another limited study on the relationship between cancer of the lung and cigarette smoking. The author's conclusion was that smoking and staying in a room laden with tobacco smoke took first place as an exogenous causal factor for cancer of the lung in males in Holland. See Tables II, III and IV for summary.

In 1950, four retrospective studies were published in the American medical literature on the relationship between smoking and the incidence of cancer of the lung.

In a study conducted by Schrek, Baker, Ballard and Dolgoff (388), the smoking habits of 82 men with cancer of the lung and 73 men with cancer of the larynx and pharynx were compared with the smoking habits of the control group of 522 patients with miscellaneous tumors. A relatively high percentage of cigarette smokers was found among the patients with cancer of the lung, larynx, pharynx and lip as compared to the control group. This positive correlation between incidence of cigarette smoking and the incidence of these cancers appeared to the authors to be both statistically and biologically



significant. The authors concluded that these data provided strong circumstantial evidence that cigarette smoking was an etiologic factor. They found no correlation between cancers of the tongue, mouth, esophagus and stomach, and smoking. The authors of this study did note that a statistical study cannot prove whether there is a cause-and-effect relationship between two factors such as cigarette smoking and lung cancer. They stated that at best, the statistical study such as they undertook could provide circumstantial evidence that such a correlation is biologically significant. Tables II, III and IV summarize the findings of Schrek, et al. (388).

Mills and Mills-Porter (287) conducted a similar study in the state of Ohio. Comparison of 444 lung cancer cases with 430 controls indicated that cigarette smoking seemed to bear a highly significant relationship to cancer of the respiratory tract but no significant relation to the incidence of buccal cancer. A similar comparison of 124 cases of buccal cancer and 185 controls indicated that the percentage of cigar and pipe smokers was almost twice as high among white male victims of buccal cancer as among appropriately selected controls; all forms of smoking were significantly higher

among victims of respiratory tract cancer than among the controls. The percentage of nonsmokers among the white male respiratory tract and buccal cancer victims was only one-fourth as high as among properly selected control groups. Tables II, III and IV summarize the findings of Mills et al. (287) with respect to lung cancer.

Levin, Goldstein and Gerhardt (258) compared 236 cases of lung cancer with 481 non-cancer patients. The data presented by these authors indicated that, in a hospital population, cancer of the lung occurred more than twice as frequently among those who smoked cigarettes for twenty-five years than among other smokers or nonsmokers of comparable age. Pipe smokers apparently experienced an increase in the incidence of lip cancer almost equal to the increase observed in lung cancer among cigarette smokers. The authors were evidently somewhat surprised to find that the type of smoking, i.e., cigarettes for lung cancer, pipe for lip cancer, was the associated factor, rather than the actual use of tobacco. The statistical association, according to the authors, may, of course, be due to some other unidentified common factor between these types of smoking in lung and lip cancer. This study was conducted

IV-B-9

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at the Roswell Park Memorial Institute in Buffalo, New York. Tables II, III and IV summarize the results of Levin et al. (258).

Wynder and Graham (474) in their 1950 paper cited various studies that had been conducted in previous years and classified them as careful but limited clinical studies. These were as follows: Adler (1451), Tylecote (449), Hoffman (179), McNally (277), Lickint (260), Arkin and Wagner (14), Roffo (351) and Maier. A brief mention was made of the statistical study of Muller (296), and the suggestions of Ochsner (311-A) were referred to. The study as published contained a comparison of 605 cases of cancer of the lung compared with 788 patients classified as "general hospital population." The authors concluded that excessive and prolonged use of tobacco, especially in the form of cigarettes, appeared to be an important factor in the induction of bronchogenic carcinoma. The data supporting this conclusion were as follows: among 605 men with bronchogenic carcinoma, other than adenocarcinoma, 96.5 percent were moderately heavy to chain smokers for many years, compared with 73.7 percent among the general male hospital population without cancer. Among the cancer group, 51.2 percent were excessive for chain smokers compared to 19.1 percent in the general

hospital group without cancer. The occurrence of carcinoma of the lung in a male nonsmoker or minimal smoker was, according to the authors, a rare phenomenon (2.0 percent). The authors suggested that the greater practice of inhalation among cigarette smokers as compared to inhalation among cigar or pipe smokers is a factor in the increased incidence of cancer of the lung. Tables II, III and IV summarize the results presented by Wynder and Graham (474).

In 1952, McConnell, Gordon and Jones (274) reported the results of a study conducted in Liverpool, England. This was a rather limited study involving cancer of the lung in 93 male patients seen between 1946 and 1949. The controls, seen between 1948 and 1950, were in-patients at the three hospitals from which the lung cancer cases were drawn and corresponded in age and sex with each of the cancer patients; the controls were not known or suspected to be suffering from any form of cancer. The authors presented the following data: Careful questioning showed that 47 percent of the cancer patients had been exposed appreciably to various dusts, fumes and smokes; 43 percent of the controls had been similarly exposed, and in approximately the same proportions. Only a slightly

IV-B-11

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higher proportion of the cancer patients lived in industrial areas (60 percent for cancer cases as compared with 54.5 percent of the controls). An equal proportion of the two groups (16 versus 17 percent) had lived near a gas works or other industrial source of atmospheric pollution.

No significant difference was found between either the incidence of smoking or the proportion of cigarette-smokers in the two groups. A significantly higher proportion (33 percent) of the smokers with cancer had smoked more than 20 cigarettes per day than had the smokers without cancer (18 percent). There was a slightly higher proportion of pipe smokers among the smokers with cancer than among the smokers without cancer. The authors concluded that heavy smoking of cigarettes may be a factor in the etiology of carcinoma of the lung. Tables II, III and IV summarize the findings of McConnell et al. (274).

Another British study, conducted by Doll and Hill (102, 103), compared 1,357 patients with cancer of the lung with 1,357 patients matched to the lung-carcinoma patients with respect to sex, with respect to the same five-year age group, and from the same hospital as nearly as possible at the same time. Only

IV-B-12

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seven of the lung cancer patients (0.5 percent) were nonsmokers as defined by the authors. From the data presented, the authors concluded that the association between smoking and carcinoma of the lung is real. They did mention tobacco smoke was not considered to be the sole cause of the increased death rate of recent years nor could it fully explain the different mortality rates between town and country. Tables II, III and IV summarize the results of Doll and Hill (102, 103).

In 1953, Sadowsky, Gilliam and Cornfield (378) presented the results of a retrospective smoking study conducted by the National Cancer Institute. The retrospective smoking histories of 1,990 patients with cancer of the lip, other oral cavity, pharynx, esophagus, larynx and lung (477 cases) were analyzed and compared with those of 615 patients with illnesses other than cancer. Comparisons were made of percentages of smokers in each group, as well as in terms of the magnitude of relative risk of cancer among smokers and nonsmokers. The findings were also compared with those of several other then recently recorded studies, namely, those of Doll and Hill (102, 103) and Wynder and Graham (474). On the basis of the general criteria employed in this study, the authors concluded that the following associations

IV-B-13

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were demonstrated in their series: (a) between pipe smoking and cancer of the lip, (b) between cigarette smoking and cancer of the larynx, and (c) between cigarette smoking and cancer of the lung. With respect to the statistical significance of an apparent realness of the associations found in this study, the authors considered that there remained the question of whether smoking was etiologically related to cancer of the lung. Tables II, III and IV summarize the findings of Sadowsky, et al. (378).

Wynder and Cornfield (473) in a limited study involving 63 physicians with cancer of the lung dying between 1949 and 1952 and 133 physicians with cancer outside the respiratory tract between 1950 and 1952 found that a highly significant association between the use of tobacco and the development of pulmonary cancer was present among these physicians. Smoking information was collected through questionnaires mailed to the next-of-kin. With respect to exposure to respiratory irritants other than tobacco among the two groups, there were no significant differences. These results, according to the authors, agreed with those of the previous studies cited above. Tables II, III and IV summarize the findings of Wynder, et al. (473).

In a Finnish study conducted by Koulumies (238), 351 pulmonary carcinoma patients in whom the diagnosis was confirmed histologically and 494 patients with pulmonary carcinoma not verified by biopsy were compared with control patients consisting of 315 persons. The conclusions in this paper referred principally to males and the pulmonary carcinoma patients were almost all smokers who had smoked heavily for decades. In comparison with the control material they had started smoking younger, often from childhood, and had smoked continuously for approximately 30 years, i.e., an average of eight to ten years longer than the patients free from cancer. According to the author, these circumstances were probably of significance in the genesis of pulmonary carcinoma. Tables II, III and IV summarize the findings of Koulumies (238).

In 1953, Lickint (673) presented a monograph on cancer of the lung. In a study presented in this paper, 224 lung cancer patients were compared with 1,000 controls. A summary of these results is shown in Table II. In a review of this monograph by Homburger published in Science (January 28, 1955, page 131), the following was noted:



"In the chapter on experimental production of cancer with tobacco products there is a wealth of older material, largely listed without critical evaluation. Nevertheless it is presented, whereas there is a tendency in the newer American literature to omit this older material altogether.

One wonders why the furore about cigarette and cancer has started only recently, when, as appears from Lickint's book, so much information on the subject has long been available, and when alarming rises in cancer of the lung have taken place for as long a period of time as seems to have been the case."

In 1954, Breslow, Hoaglin, Rasmussen and Abrams (615-A) compared 518 male lung cancer cases with 518 patients not suffering from cancer or a chest disease. The cancer cases and controls were matched for sex, age and race. The data presented in this study, besides suggesting that cigarette smoking is linked with lung cancer, also suggested that several occupations have an etiological relationship in the development of cancer of the lung. These occupations were welding, sheet metal working, steam fitting, boiler making, asbestos industry, hot metal industries, oilers, firemen, painters, and cooks. Seventy-seven of the total lung cancer patients (numbering 518) were involved in these suspected occupations. The authors stated that their data clearly showed that cigarette smoking was more frequent and more intense among lung cancer patients than among the control group. The authors cited many of

the preceding studies mentioned above. Tables II, III and IV summarize the findings of Breslow et al. (615-A).

Watson and Conte (460, 719-A) published two papers in which a definite relationship between heavy cigarette smoking and cancer of the lung was claimed. However, they did consider that further studies were necessary to furnish more precise estimates of the risk involved in smoking. The authors did discuss some of the criticism of the various retrospective studies. In these studies (460, 719-A), the controls were patients suffering from diseases other than cancer of the lung. Tables II, III and IV summarize the results presented by Watson and Conte (460, 719-A).

Gsell (575) conducted a retrospective study in Switzerland. As may be noted from the summary in Table II, the results of this study paralleled those discussed previously. The number of lung cancer cases in this study was 135 and the number of matched controls was also 135.

A retrospective study conducted by Randig (1059) in Germany gave essentially similar results. A summary is given in Table II.

Stocks and Campbell (1104-A) compared death rates from lung cancer observed during the period 1952-

1954 among men 45 to 75 of different smoking habits resident in rural, mixed and urban areas, and related them to measurements of 3,4-benzpyrene and other substances in the air at various places in these areas; they estimated that half of Liverpool lung cancer deaths resulted from cigarette smoking and three-quarters of the remaining half to a factor only slightly present in rural areas. They suggested that 3,4-benzpyrene plays a dual role through cigarettes and air pollution. This paper will be discussed in greater detail in the section on environmental aspects of the etiology of respiratory cancer.

Three newer retrospective studies conducted subsequent to the prospective studies (153, 2534-A, 2534-B, 628-B, 918-D, 2761) have been reported recently. One was by Schwartz and Denoix (2658, 2658-A), who conducted an investigation based on 602 cases of cancer of the lung, including 407 cases with a histological or cytological diagnosis, 56 with a histological diagnosis but without determination of the exact histological type, and 139 cases with a clinical diagnosis. A study was made of the role played by tobacco in patients suffering from lung cancer; the findings were compared with those in four other groups of population. The

IV-B-18

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smokers were classed into different categories according to the duration of the habit of smoking: 5 years, 10 years; and according to the amount of tobacco smoked per day (less than nine cigarettes per day, 10-19 cigarettes per day, 20-29 cigarettes per day, more than 30 cigarettes per day). The three groups gave entirely comparable results. Among those suffering from lung cancer, the number of smokers was found to be higher than among the controls. The cancer patients smoked more cigarettes than pipes and smoked more in each category than the controls.

The other two recent retrospective studies are one by Segi et al. (2659-A), and one by Stocks (2900-A).

Wynder, Bross and Day (1135, 1135-A) compared 209 white males with cancer of the larynx seen at Memorial Center with 209 controls with cancer of other sites from the same hospital matched for age, religion, sex, education and hospital status, and 132 cases of lung cancer unmatched except for sex. Data were collected by interviews upon admission. Fewer non-smokers were found among lung cancer cases and larynx cancer patients than among controls; the relative risk for laryngeal cancer was said to increase in proportion to the amount smoked, and the risk increased in smokers with the consumption of 7 oz. or more of whiskey or equivalent per day. Some

IV-B-19

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other factors were also discussed.

Wynder, Hultberg, Jacobsson and Bross (2100) found tobacco of all types important in the development of cancer of the upper alimentary tract, hypopharynx, esophagus and larynx.

Wynder, Bross and Feldman (2446) compared 659 white male and female patients with cancer of the oral cavity seen at Memorial Center with 439 control patients with benign diseases and cancer of other sites at the same hospital. There was some matching of groups with respect to age and religion. The data were collected by interview, the diagnosis being unknown to the interviewer in the majority of cases. The per cent non-smokers among males with oral cavity cancer was 3, among controls 10; the per cent of "excessive" smokers among males with oral cavity cancer was 29, among controls 17. Twice as many non-smokers were found among female controls as among females with cancer of the mouth, and three times as many "chain smokers" were found among females with cancer of the mouth as among controls. Other factors were discussed.

Wynder, Navarrete, Arostequi, and Ilambes (2722) compared 399 male and 107 female clinic patients with cancer of the respiratory tract to 220 male and 214 female control clinic patients, seen between 1956 and 1957,

IV-B-20

2025018144

matched for age. The data were collected by interview. Three per cent of the male study cases were non-smokers compared to 16 per cent among the controls; the respective percentages for females were 13 and 66 per cent; "significantly more heavy smokers" were among the study cases.

Wynder and Lemon (3372, 3858-A) in 1958 compared 564 Seventh-day Adventist cancer and coronary artery disease patients in 8 Seventh-day Adventist hospitals with 8,128 non-Adventists having the same diseases in the same hospitals. Background data were gathered from 460 Adventists (261 males, 199 females). Seventy-one per cent of Adventist males over 40 never smoked, and only 6% smoked more than 20 years; in the general population sample 85.4% smoked more than 20 years. Seventy-seven per cent of the sample never drank. Low consumption of meat, coffee and tea relative to the general population was noted. There were 118 lung cancer cases among the non-Adventists. Only 1 Adventist lung-cancer patient was found; he smoked previously to joining the church. There were 133 lip, esophagus, and mouth cancers among non-Adventists and only 1 (a lip cancer) in an Adventist. Since a large portion of the non-smokers came from Southern California, it was concluded that smog had no significance in the causation of lung cancer. It

IV-B-21

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was also concluded that a common factor could hardly cause both cancer and desire to smoke since it would also have to prevent becoming an Adventist. The study found coronary artery disease much less prevalent among Adventists, too.

In 1959, Lombard and Snegireff (3486) compared 500 male lung cancer patients as to smoking habits and other characteristics with several control groups (totalling 4811 persons and consisting of 500 hospital patients, 500 persons in the same economic group as the cancer patients, 500 members of certain organizations and employees in certain vocations, a random urban selection (339 matched to 339 patients), 1,723 cancer clinic patients, 272 rural residents over 40, and 404 urban residents over 40). Per cent cigarette smokers: lung cancer patients, 95%; control groups, 55 - 80%; combined controls (average of the first four groups listed above); 75%. Non-smokers; cancer patients, 1 1/2%; control groups, 5 1/2 - 17%; combined controls, 10%. Pipe and cigar smokers only: cancer patients, 4%; control groups, 13-28%; combined controls, 14.5%. Heavy smokers (over 9,125 packs during lifetime): cancer patients, 68.5%; combined controls, 42.5%. Whether a smoker inhaled or not made a significant difference in the rate of lung cancer among light smokers but less among heavy

IV-B-22

2025018146

smokers. Persons with previous respiratory ailments, heavy users of alcohol, and people who worked out of doors had higher lung cancer rates than people without these characteristics and constituted 1/3, 1/7, and 1/5 of cancer patients, respectively.

The retrospective studies summarized in the preceding paragraphs pertain chiefly to white males [cf. Watson and Conte (719-A) and Doll and Hill (103)]. The sex disparity, accepted in the past as a very strong argument against the cigarette smoking-lung cancer theory, has been jolted by several recent statistical studies reporting lung cancer in women. There are four such studies, by Doll and Hill (103), by Watson and Conte (719-A), by Wynder et al. (1300) and by Haenszel et al. (2792, 3130). They are all retrospective in approach. A summary of them is printed in Table V taken from Haenszel et al. (3130). As may be seen, the numbers in each study are relatively few; in fact, fewer than in one of the male retrospective studies criticized by Wynder and Graham (474) as being limited, i.e., the study of Muller (296).

All four studies reach the same conclusion, viz.: that cigarette smoking is associated with lung cancer in women. They also conclude that the prevailing excess mortality among males almost disappears when



TABLE V

"COMPARISON OF DATA ON HISTOLOGIC TYPE AND  
SMOKING HISTORY REPORTED IN 4 CONTROLLED RETRO-  
SPECTIVE STUDIES OF LUNG CANCER AMONG WOMEN

[Note: Table 6 of Haenszel and Shimkin (3130)]

	<u>Microscopically confirmed cases</u>		<u>Percent of nonsmokers among</u>			
	<u>Number</u>	<u>Percent classified as adeno-carcinoma</u>	<u>All cases</u>	<u>Not</u>		
				<u>Adeno-carcinomas</u>	<u>adeno-carcinoma*</u>	<u>Controls</u>
United States:						
Present study	158	35	51(59)**	66(71)	43(53)	69(77)
Wynder <u>et al.</u>	105	39	56	71	38	74
Watson and Conte	36	***	58	***	***	82
England and Wales:						
Doll and Hill	79	13	37	50	35	55

\* Includes 'epidermoid,' 'undifferentiated,' and 'anaplastic,' but excludes carcinomas of unclassified type.

\*\* Two results on the proportion of nonsmokers are shown for the present study - one based on lifetime history and the other, in parentheses, reflecting status before onset of illness. The data of Wynder et al. and Doll and Hill refer to lifetime history. The Watson and Conte determination of smoking status was not stated.

\*\*\* Data not reported by histologic type."

2025018148

nonsmokers are studied. The remaining excess is consistent, they argue, with the well-known fact that males have a greater mortality than females for most diseases, which prompts Haenszel et al. (3130) to conclude that no sex-linked factor need be postulated for the difference in lung cancer deaths. They claim, moreover, that their study and the others indicate a lower proportion of non-smokers among patients with epidermoid and undifferentiated carcinomas in the face of a close correspondence between those with adenocarcinomas and the controls. This is consistent with the theory espoused by Wynder, and others, that epidermoid carcinoma is associated with smoking to a greater degree than adenocarcinoma.

Finally, Haenszel et al. (3130) attack as fallacious (in view of the disparity between epidermoid and undifferentiated carcinoma and adenocarcinoma in degree of association with smoking history) the use of published mortality data lacking in distinction between histologic types to demonstrate inconsistencies in the cigarette theory by noting incommensurate sex differences in rate of increase of total lung cancer mortality and in rate of adoption of the smoking habit.

In 1956, Wynder, Bross, Cornfield, and O'Donnel (1300) compared 105 patients with lung cancer between 1950 and 1955 at 11 different hospitals with 1304 cases with

tumor or cancer of sites other than respiratory and upper alimentary tract seen at a New York City hospital; data were obtained by interview or questionnaire directed to a friend or relative in lung cancer cases and by interview from the controls; diagnosis known; fewer non-smokers among the epidermoid lung cancer cases than among the controls, more persons smoking a pack or more of cigarettes a day among epidermoid lung cancer cases than among controls; other factors discussed.

Aside from the criticism of these studies which might be made on the ground of the small number of samples studied, it is noteworthy that Haenszel et al. themselves acknowledge at least the need for further study, in the following guarded language:

"The data available for women seem consistent with the hypothesis of an etiologic relationship between cigarette smoking and the occurrence of epidermoid and undifferentiated carcinoma of the lung, but further studies of sex differences, in risk by histologic type, smoking class, occupation, and other factors, should be pursued to elaborate additional facets of lung-cancer epidemiology."

IV-B-25

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b. Prospective

The results of three prospective studies have been published. The preliminary report (153) of Hammond and Horn's study under the auspices of the American Cancer Society was published in 1954, and the subsequent reports in 1958 (2534-A, 2534-B). Doll and Hill's (628-B, 918-D) work in England was published in 1954. Dorn's study, sponsored by the U. S. Public Health Service, was first presented in 1958.

Hammond (650, 650-D) has been critical of the retrospective studies in general, and of the studies of Breslow et al. (615-A), Doll and Hill (102), Levin et al. (258, 631), Watson and Conte (460) and Wynder and Graham (474) in particular. However, he does admit that the results of these retrospective studies are highly suggestive of an association between lung cancer and smoking (2244). He believes that these results, together with the results of the prospective and biological studies, constitute proof of a cause-and-effect relation, which he defines as follows (2244):

"My definition of causation is something like this: A causative factor for a disease is any factor which in a given situation increases the probability that the disease will develop. A causal factor for an event is any factor, the presence of which increases the probability of that event occurring."

This definition, having statistical overtones, was given by him at a Sigma Xi lecture in Raleigh, N. C., which was taped. Subsequently, on publication of this lecture in "American Scientist", the Sigma Xi magazine, the definition was not included.

IV-B-27

2025018152

(1) Hammond and Horn

In 1954, Hammond and Horn (153) published their first findings on a study conducted of 187,766 white males under the auspices of the American Cancer Society. Some 200,000 white males were questioned by American Cancer Society volunteers as to their smoking habits, and then their histories were followed over a period of approximately four years. Each of the volunteers was to question ten white males, age 50-69, who were not sick and from whom follow-up information could be obtained.

The first publication by Hammond and Horn (153) covered the initial 20-month period of the study. It was found that men with a history of regular cigarette smoking had a considerably higher death rate than the men who had never smoked or men who had smoked only cigars or pipes. A total of 3,002 deaths occurred among the men with a history of regular cigarette smoking. If these men had died at the same rate as the men who never smoked, only 1,980 would have died. Thus, 1022 additional deaths (52 percent more than expected) occurred among men with a history of regular cigarette smoking. The death rates increased with the amount of cigarette

smoking. A total of 745 deaths occurred among the males who were currently smoking a pack or more of cigarettes a day at the time they were first questioned. Only 426 of them would have died if their death rates had been the same as for the men who never smoked. Thus, an additional 319 deaths (75 percent more than expected) occurred among the males who were smoking a pack or more of cigarettes a day at the beginning of the study.

Cancer was indicated as the primary cause of death of 844 males, 18 percent of those for whom death certificate information was available. Deaths from cancer were said to be definitely associated with regular cigarette smoking, the effect being particularly marked in the older age groups. Approximately 26 percent of the total effect of cigarette smoking on the over-all death rate was attributed to the effect of cigarette smoking on deaths from cancer. The findings were said to suggest that there might also be a relationship between the use of cigars and pipes and death rates from cancer.

Of the 844 deaths due to cancer, 167 were indicated on the death certificates as being due to cancer of the lung. The death rate from lung cancer was

much higher among men with a history of regular cigarette smoking than among men who never smoked regularly. Regular cigarette smokers had a higher death rate from cancer of sites other than the lung than did men who never smoked.

According to the authors, these findings proved that there was a definite association between smoking habits and death rates, at least in white men between the ages of 50 and 69; most of the overall association was accounted for by an association between regular cigarette smoking and death rates from cancer and from diseases of the coronary arteries, although it was said to be possible that some other diseases may also be involved. The authors were of the opinion that the associations found in their study between regular cigarette smoking and death rates from the diseases of the coronary arteries and between regular cigarette smoking and death rates from cancer of the lung reflected a cause-and-effect relationship.

In 1958, Hammond and Horn published two papers in which the data in the preceding paper (153) were extended to a time period of 44 months (2534-A, 2534-B). In the later papers, particular attention was given to the possible sources of bias in the data. With respect to this 44-month study the authors summarized their find-

2025018155



ings as follows:

Age being taken into consideration, the death of males with a history of regular cigarette smoking only was found to be 68 percent higher than that of a comparable group of males who never smoked. The death rate of cigarette smokers increased with the amount of cigarette smoking. Among men with a history of regular cigarette smoking only, the death rate based on "mortality ratios" (see below) of those smoking two or more packs of cigarettes a day in 1952 (the beginning of the study) was 123 percent higher than that of males who never smoked. Also, the death rate of males with a history of regular cigar smoking was only 22 percent higher than that of males who never smoked, and the death rate of males with a history of regular pipe smoking only was 12 percent higher than that of males who never smoked.

The death rate of males who had smoked only occasionally was not significantly different from the death rate of males who never smoked, and the death rate of males who had given up cigarette smoking for a year or more before being enrolled in the present study was lower than that of males who were smoking cigarettes regularly at that time.

The findings in the latter two years of this study, according to Hammond and Horn, fully confirmed

the findings previously reported for the earlier part of the study (153). The authors concluded that due to the many checks that were made to determine the reliability of the findings, they could find no errors or biases which would have a serious effect on the over-all results.

There was a high degree of association between total death rates and cigarette smoking, a far lower degree of association between total death rates and cigar smoking, and a small degree of association between total death rates and pipe smoking. The available source of information for this study, on diseases involved, was cause of death as recorded in death certificates, supplemented by more detailed medical information in cases in which cancer was mentioned. These reports were based on 11,870 reported deaths. The results were summarized in terms of "mortality ratios", obtained by dividing "expected" deaths (the number which would have occurred among men in each smoking category if their age-specific death rates had been the same as those for non-smokers) by "observed" deaths (the actual numbers of deaths occurring in each smoking category). The number of deaths reported for "well-established" bronchogenic carcinoma "exclusive of adenocarcinoma" was 295: 4 occurred among 32,392 non-smokers, 5 among 11,703 occasional smokers, 162 among 63,632 smokers of

2025018157

cigarettes only, and 103 among 44,136 smokers of cigarettes and cigars and/or pipes; among cigarette smokers only, 13 lung cancer deaths occurred among 7,647 smokers of less than one-half pack a day, 50 among 26,370 smokers of one-half to one pack a day, 60 among 14,292 smokers of one to two packs a day, and 22 among 3,100 smokers of more than 2 packs a day. Lung cancer death rates were expressed in terms of "100,000 man years standardized to the age distribution of the white male population of the United States as of July, 1954." The lung cancer death rate for non-smokers was 3.4, for cigarette smokers only, 78.6; for cigarette smokers the lung cancer death rates according to amount smoked daily were: less than one-half pack, 51.4; one-half to one pack, 59.3; one to two packs, 143.9; two or more packs, 217.3.

The authors listed the following relationships with cigarette smoking: (a) an extremely high association for a few diseases, such as cancer of the lung, cancer of the larynx, cancer of the esophagus, and gastric ulcers; (b) a very high association for a few diseases such as pneumonia and influenza, duodenal ulcer, aortic aneurysm, and cancer of the bladder; (c) a high association for a number of diseases, such as coronary artery disease, cirrhosis of the liver, and cancer of several sites; (d) a moderate association for cerebral vascular

lesions; and (e) little or no association for a number of diseases, e.g., chronic rheumatic fever, hypertensive heart disease, diabetes, leukemia, etc. The relative reliability of the association listed previously is dependent on the number of deaths attributed to each disease, as well as on their degrees of association with cigarette smoking.

It was found that the death rate of males with lung cancer who had given up cigarette smoking for a year or more before being enrolled in the study was lower than the death rate of males who were smoking cigarettes regularly at that time. An extremely high association between cigarette smoking and death rates from males with this disease was found in rural areas as well as in large cities. When smoking habits were taken into consideration, the lung cancer death rate was still somewhat higher in urban areas than in rural areas.

(11) Doll and Hill

Doll and Hill, in England, published the results of a similar prospective study conducted on the physicians in England. The first report of this study was presented in 1954 (628-B) and the second report was published late in 1956 (918-D). The authors' summary and conclusions presented in the later paper were:

"In reply to a questionnaire sent out at the end of 1951, over 40,000 males and females on the British Medical Register informed the authors of their smoking habits at that time or, in the case of ex-smokers, when they previously gave up smoking. On the basis of the answers, the authors classified them into a few broad groups, namely, nonsmokers and smokers (or ex-smokers) of three different amounts by cigarette, pipe, or both. The subsequent mortality of each of these groups was recorded for nearly four and one-half years. This study related to males age 35 years and above amongst whom there were 1,714 deaths, including 81 from cancer of the lung (in 3 others, cancer of the lung was mentioned as a contributory cause).

"The analysis showed that in this population there was a marked and steady increase in death rate from cancer of the lung as the amount smoked increased. Its death rate per year rose from 0.07 per 1000 in nonsmokers (based upon the observations of one death only) to 0.47 per 1000 in light smokers of 1-14 grams a day, to 0.86 per 1000 in medium smokers of 15-24 grams a day, and finally to 1.66 per 1000 in smokers of 25 grams or more a day (1 gram being almost equivalent to 1 cigarette). The death rate of the heavy smokers was approximately 20 times the death rate of the nonsmokers.

"This rising mortality from lung cancer in smokers compared with nonsmokers, and in heavy smokers compared with lighter smokers, was a feature of each stage of life, 35-54 years, 55-64 years, 65-74 years, and 75 years and over.

"The mortality from lung cancer was substantially and significantly greater in cigarette smokers than in pipe smokers, with smokers by both methods falling in between. This difference between pipe and cigarette smokers was observed for each of the smoking categories; light, medium, and heavy, and therefore appeared to be a function of the method of smoking irrespective of the amount smoked.

"Those who reported themselves as smokers on November 1, 1951, were compared with those who had given up smoking at that time within the previous 10 years or for more than 10 years. The comparison revealed a progressive and significant reduction in mortality with the increase in the length of time over which smoking had been given up.

"From these conclusions, it follows that the highest mortalities have occurred amongst those persons who reported themselves as continuing to smoke on November 1, 1951. Among them, the annual death rate rose from 0.95 per 1000 for smokers of 1-14 cigarettes per day, to 1.67 per 1000 for smokers of 15-24 cigarettes per day, and to 2.76 per 1000 for smokers of 25 cigarettes or more per day, i.e., to approximately 40 times the death rate of the nonsmokers.

"For every death attributed to cancer of the lung confirmation of the diagnosis was sought from the certifying doctor and, when necessary, from hospital or consultant. Additional information was obtained in every case. The deaths were thus divided into those quite firmly established by necropsy, histological evidence, and the like, and those less well established and lacking histological evidence. The increased death rate associated with the increase in smoking was found to be just as great with the firmly established cases as it was with the remainder. The relationship could not therefore be attributed to a biased attitude in the medical profession in certifying cancer of the lung as the cause of death.

"Analysis of the deaths from lung cancer separately in each of the first four years of the inquiry showed that the increase in mortality associated with an increase in smoking was a feature of each year. On the whole, there was a remarkably con-

stant gradient which became no less marked with the passage of time. The authors also estimated that in the fourth year of the inquiry the mortality of the doctors who answered the questionnaire was as much as 92 percent of the mortality of all doctors whether they answered the questionnaire or not. On these grounds the authors did not believe that the gradient of mortality with smoking could be regarded as merely an artifact due to bias in those who chose to reply to the questionnaire.

"An analysis of a random sample of the questionnaire showed that there was remarkably little difference between the smoking habits of doctors resident (at November 1, 1951) in greater London, in large towns, or in other districts. The contrast in lung cancer mortality between smokers and nonsmokers, and between light, medium, and heavy smokers, could not therefore be attributed to a differential exposure to atmospheric pollution which happened to be associated with smoking habits. This observation supported those of previous investigations.

"Study of the deaths in sites other than the lung revealed, with one possible exception, no association between mortality and smoking (cf. the results of Hammond and Horn). The exception is cancer of the upper respiratory and upper digestive tracts, from which the number of deaths was in 1956 insufficient to substantiate a possible trend. Total cancer of sites other than the lung showed a mortality of 2.04 per 1000 in nonsmokers and 2.02 per 1000 in smokers. No gradient was revealed by the amount smoked. In other words, the marked and steadily increasing mortality from cancer of the lung in association with smoking was not compensated for by a decrease in cancer of other sites. The result indicated a total mortality from cancer in the smoking groups in excess of the mortality that would have prevailed in the absence of smoking.

"If the causes of death as certified were accepted at their face value, mortality from coronary thrombosis revealed a slight but significant relationship with smoking. Division by age, however, showed that the trend is distinct only at the youngest ages, 35-54 years.

"Three other causes of death show a steady increase in mortality from nonsmokers to heavy smokers. These were deaths due to chronic bronchitis, peptic ulcer and pulmonary tuberculosis. Only with chronic bronchitis was the gradient statistically significant. The remaining causes of mortality revealed no trend."

The authors then noted that from the results of their retrospective studies (102, 103) of the smoking habits of some 1500 patients with lung cancer and over 3000 patients with other diseases, they had concluded that if large groups of persons of different smoking habits were observed for a number of years they would reveal distinct differences in the rates of mortality from lung cancer. These differences would show (a) a higher mortality in smokers than in nonsmokers, (b) a higher mortality in heavy smokers than in light smokers, (c) a higher mortality in cigarette smokers than in pipe smokers, and (d) a higher mortality in those persons who continue to smoke than in those who gave it up. In each case the expected result appeared in the prospective inquiry reported in 1956. These results were evident in spite of the fact that the method of inquiry was such as constantly to underestimate the mortality difference. The reason for the underestimate is that the authors' classifications were based, for the most part, upon a statement of the smoking habits of one point of time. The authors seldom were able to take previous habits into account,



and any subsequent changes were thus unknown to them. As a result the authors may have sometimes included in the light smoking group persons who had previously smoked heavily for a long time; sometimes a pure pipe smoker would have been classified as such when he had previously smoked cigarettes and vice versa; sometimes a person classed as a smoker would still be classed as a smoker when he had given up the smoking habit. All such errors in classification, according to the authors, must inevitably have reduced the extent of the association between the mortality of cancer of the lung and the smoking of cigarettes which were observed in the British doctors.

IV-B-39

2025018164

(iii) Dorn

In 1958, the third prospective study, by Dorn (2761), was presented. This report summarized the mortality experience of 198,926 policy holders of U.S. government life insurance from July, 1954 to December, 1956. All of the policy holders had served in the armed forces of the United States between 1917 and 1940. Over 99 percent were males; 84 percent were 50-70 years of age. The total number of deaths in the whole sample was 7,382.

The author found that deaths from all causes of persons who had used tobacco was 32 percent greater than for persons who had never smoked. Persons who had regularly smoked only cigarettes had the highest death rate of all groups of smokers, 58 percent greater than the rate for nonsmokers. The death rate of persons who had regularly smoked cigars and/or a pipe was not appreciably higher than that of nonsmokers. Regular cigarette smokers who had stopped smoking cigarettes prior to the beginning of the study in 1954 had a lower mortality rate than those who had continued to smoke. However, this rate still was 31 per cent greater than that for nonsmokers. The excess of mortality of regular cigarette smokers was greater for heavy smokers than for light smokers. Only the heavy users of cigars and pipe tobacco experienced a significant increase in total mortality over that of persons who had never smoked.

The greatest increase for smokers in the risk of developing a disease was for lung cancer. The mortality ratio for regular smokers of cigarettes only was 9.85, or approximately ten times that for nonsmokers. Regular users of cigars and/or pipes showed an increased mortality rate from cancer of the lung as well as from all forms of cancer as a group but this increase was much less than that for cigarette smokers. Regular cigarette smokers also were subject to an increased risk of dying from cardiovascular diseases, from certain respiratory diseases such as bronchitis, pleurisy and emphysema, from ulcers of the stomach and duodenum, and from cirrhosis of the liver. The death rate from coronary heart disease among regular users of cigarettes only was 63 percent higher than the rate for nonsmokers.

In 1955, Cutler (777) reviewed the available statistical evidence on the association between smoking and lung cancer. Fourteen of the retrospective studies were reviewed; Tables III and IV herein indicate Cutler's summary of these studies. In addition, Cutler considered the two prospective studies from which preliminary data had been reported. He summarized his review as follows:

"The available evidence on the relationship between smoking and lung cancer is of four kinds: (a) The observed concomitant increase in recorded mortality from lung cancer and

consumption of cigarettes. (b) Fourteen case history studies. (c) Table III (indicating a smaller percentage of nonsmokers and a higher percentage of heavy smokers among lung cancer patients than among comparable controls). (d) Preliminary results of two population studies [Hammond and Horn (153) and Doll and Hill (628-B)] indicate a higher incidence of lung cancer in smokers than in nonsmokers, and a still higher incidence in heavy smokers. (e) The successful production, by at least one team of investigators, of skin cancer in animals with condensates of tobacco smoke [475]."

Cutler then concluded:

"There is disagreement whether the evidence at hand warrants a conclusion that smoking and lung cancer are causally related. As additional evidence is gathered from observation of human populations and from experimentation with animals, conclusions will be reached which should achieve general acceptance."

IV-B-42

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### 3. SUMMARY OF STATISTICAL STUDIES

The statistical considerations of any type, i.e., retrospective or prospective, of the lung cancer-cigarette smoking question lead to or are considered to lead to several general conclusions, most of which must be viewed with disfavor by the Tobacco Industry. These general conclusions, which state the case in the most favorable light possible for the adherents of the tobacco theory, are set forth below. None, however, can be taken in our opinion as axiomatic at this stage of learning; they are set forth here so the reader can see the claims made against tobacco, and the basis for them. The explanation for or answer to each of these will be set forth later.

1. The incidence of lung cancer in the human male has increased markedly during the past half century in practically every civilized country of the world even when consideration is taken of the increased life span of the individuals. There are dissenting opinions, e.g., those of Rigdon (1911-A), Hueper (970-B) and Gilliam (944-A), to various aspects of this argument.

2. The increase in incidence of cancer of the lung in the human male parallels, after due

consideration is given to a suitable latent period, the increase in consumption (or production) of cigarettes. (This is a favorite hypothesis of Ochsner, et al. (309, 590, 696-D, 1037, 1038, 1859-N, 3173, etc.)). Many persons with dissenting opinions as to this hypothesis list many other commodities whose production has likewise increased remarkably during the past half century, e.g., fuel oil, gasoline, automobiles, etc.

3. Cigarette smokers, according to the statistical studies, exhibit a significant and distinctly higher liability to respiratory cancer than nonsmokers. The incidence of cancer of the lung and larynx is more or less directly proportional (a) to the number of cigarettes smoked per day, (b) to the duration of the smoking habit, and (c) to the amount or degree of inhalation practiced by the smoker. Of course there are numerous criticisms of the statistical studies. See, infra.

4. Cigarette smoking is more closely associated statistically with squamous-cell carcinoma of the lung than with adenocarcinoma (670, 1300, 3130). Squamous-cell carcinomas of the bronchi were rarely seen before the advent of the cigarette

smoking habit. Their recent marked increase in males in particular is said to be the result of carcinogenic components of cigarette smoke (cf. Hueper (970-B)).

5. The reason for the high male:female ratio in the incidence of cancer of the lung is presumably due to the fact that women have been smoking neither as much nor for as long a time as the males. When due consideration, however, is given to the amount of smoking, cancer of the lung in women is also increasing and particularly in the case of the squamous-cell-type (3130).

6. The site of contact of tobacco smoke and the development of cancer, e.g., the lung for cigarette smokers due to greater tendency to inhale; the mouth, lip and/or larynx for cigar and pipe smokers due to the tendency of noninhalation, is alleged to be in agreement with the known factual data on carcinogenic processes (observed in animals).

7. The higher lung cancer rates among urban populations compared with rural populations are attributable to the greater increase and more general consumption of cigarettes by the former, which in turn increases, like the lung cancer rate, in proportion to the size of the community. The lung cancer

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rates of urban and rural populations approach parity when the factor of cigarette smoking is eliminated (cf. Stocks and Campbell (1104-A)).

8. Although only minor fluctuations in the mortality rates of laryngeal cancer occurred during the greater part of the period of the increase in lung cancer, morbidity rates for laryngeal cancer are alleged to have increased during recent years, thereby following the lung cancer pattern. Mortality rates for laryngeal cancer have been kept stationary or even have been lowered because of improved treatment (here again there is disagreement); hence, laryngeal cancer has a positive statistical and causal relation to cigarette smoking. All parts of the respiratory tract (except the trachea) respond to the supposed carcinogenic action of cigarette smoke.

9. The disparity observed between the lung cancer mortality rates and the relative amounts of cigarettes consumed in the United Kingdom and the United States is attributed to a more economical use of cigarettes by the British smoker who thereby inhales a greater amount of "tar" than his American counterpart.



10. Cigarette smoking is responsible for 80-96 percent of all male lung cancer deaths.

In addition to the statistical evidence, other evidence is available which is presumed to support the statistical data. This will be mentioned briefly at this point. Subsequent sections of this memorandum will treat this evidence more fully.

1. Demonstration of the presence in cigarette smoke of various known carcinogenic compounds, e.g., 3, 4-benzpyrene, 3, 4, 8, 9-dibenzpyrene, 3, 4, 9, 10-dibenzpyrene, 1, 2, 5, 6-dibenzanthracene, etc.

2. Production of skin cancer in various species and strains of animals by administration of cigarette smoke condensates.

3. Disappearance of fluorescent materials from cigarette smoke on inhalation and appearance of fluorescent material in the cells lining the lungs of the host exposed to cigarette smoke.

4. The greater number of cellular changes observed in portions of the respiratory tract of heavy smokers when compared with light smokers or nonsmokers is considered to be evidence in support of precancerous changes in the lung.

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#### 4. CRITICISMS OF STATISTICAL STUDIES

The statistical data presented in the retrospective studies (102, 103, 238, 274, 287, 296, 258, 378, 388, 456-A, 473, 474, 575, 673, 460, 719-A, 1059, 1078, 615-A, 1104-A, 2658, 2658-A) involving males and those involving females (1104-A, 1300, 3130) and the prospective studies (153, 628-B, 918-D, 2534-A, 2534-B, 2761) appear at first glance to be almost overwhelming. Essentially, the general conclusions reached in these studies are the same. However, there are numerous points from different papers in these series which are open to criticism. The main body of critics consists of the following persons: Little, Hartnett, Berkson, Neyman, Arkin, Fisher, Greene, Hueper, Macdonald, Rigdon, and Rosenblatt. In a recent review by Cornfield, et al. (3409), the main criticisms of the abovementioned persons were supposedly answered.

The validity of the findings on these extensive statistical investigations has been challenged as follows:

- (a) the methods of selection of the samples is faulty;
- (b) the accuracy of information regarding (i) smoking habits and (ii) the diagnosis of the cancer of the lung is questionable;
- (c) other possible associations were not studied, or if studied, not emphasized; and
- (d) the reality of the apparent increase in lung cancer incidence is open to question.

a. Selection Bias

Berkson (875, 2463), (in 1955 and in 1958) one of the most outspoken critics of the statistical studies, indicated that people with two specific complaints are more likely to be hospitalized than people with only one of these complaints. If a retrospective study were conducted exclusively on hospital patients an association would be found between these two specific complaints, even if there were no association between the same two complaints in the general population. This would necessarily influence the results if smokers with cancer of the lung are more likely to be hospitalized than non-smokers with cancer of the lung. However, Berkson showed that this difficulty is trivial if a high percentage of people with either one of these two conditions is hospitalized, which, according to Cornfield, *et al.* (3409), is the situation with the lung cancer patients. Furthermore, one retrospective study, that of Stocks and Campbell (1104-A), included all lung cancer patients who were in the study area, including those not hospitalized; another retrospective study, that conducted by Wynder and Cornfield (473), was based on individuals who died of lung cancer and other diseases regardless of whether they had been hospitalized or not. This difficulty did not arise in the prospective studies.

Berkson also questioned the Hammond-Horn mortality ratio discussed previously. Such a ratio measures the effect of smoking on the basis of the number of deaths rather than against the living population which enhances the theory being advanced and tones down association with other factors.

Other authors (2463, 3847-A) have discussed the sampling techniques of the studies under discussion. They stated that, short of a random sample, smokers and non-smokers must be sampled in proportion to the size of those groups in the general population. If they are not, serious distortions can result. In addition, diseases of multiple etiology cannot be completely investigated by tracing two randomly selected groups, one exposed to a factor, the other not. The follow-up will only reveal that some nonsmokers can develop cancer.

Yerushalmy et al. (4018) in 1959 commented on difficulties of selecting truly comparable control groups in retrospective studies and pointed out that in a prospective study:

"The groups under observation and comparison are not selected by the investigator in a random procedure, but the individuals in the two groups have made for themselves the critical decision of acquiring the characteristic. As a result, great doubt often exists as to the comparability of the two groups. In many cases a question arises as to whether the characteristic under study may not in fact be a mere axis of

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classification -- an index which differentiates the two groups in terms of many important factors, and that these rather than the characteristic under investigation are causally related to the disease.

For example, when a sample of the population (even if randomly selected) is divided into smokers and non-smokers and the two groups are observed for the occurrence of cancer of the lung, the habit of smoking may serve only as a differentiating index for the two groups. Persons who become smokers may differ in many respects from those who elect to be non-smokers. It is perhaps these unknown factors which may be related to the occurrence of cancer of the lung, much as in the situation where an organism may accompany the real causative agent but be harmless in itself (like sarcinae in gastric cancer).

To use a more familiar illustration, only a decade or so ago many evaluations of immunizing or therapeutic agents utilized volunteers as the study group, while persons who refused to volunteer for treatment were used as controls. Few today would be willing to accept the latter as controls for the volunteers.

On the other hand, many investigators, including Professor Hill, feel that recent prospective studies lend strong support to the thesis that smoking is not only associated with, but is a cause of cancer of the lung. Yet it is difficult to perceive a basic difference in methodology in the two situations. Both suffer from the same fundamental weakness -- the factor of self-selection.

The reason that nonvolunteers are not acceptable as controls for volunteers must be the belief that volunteering per se represents an index -- an axis of classification -- which differentiates the two groups according to many factors which may have a bearing on the occurrence of the disease. The volunteer may be of the type of person who takes better care of his health and who may be a more careful

person in general. As a consequence, he might be likely to experience less of the disease in question than the nonvolunteer, even if he were not immunized. Differences in morbidity from the disease between volunteers and nonvolunteers thus may not be due to the effectiveness of the vaccine being tested, but to differences in the personalities and modes of life of the two groups.

It follows by similar reasoning that the experiences in lung cancer mortality of smokers and of nonsmokers may not logically be compared to assess smoking as the cause of the disease. Smoking, like volunteering, may represent an index which differentiates the two groups in many aspects of mode of life and perhaps also on constitutional grounds. Consequently, smokers may experience risks of death from cancer of the lung different from those of non-smokers, even if they never smoked at all. That is, people who eventually become smokers may possess certain characteristics which make them more vulnerable to certain diseases than persons who are in the category of 'non-smokers.' Smoking by itself, as an etiologic factor in lung cancer, may be the analogue of the 'satellite,' the accompanying organism of other disease situations."

In all but one of the 21 retrospective studies, the procedure involved was to compare the smoking habits of lung cancer patients with the smoking habits of a control group who did not have cancer of the lung. Hammond himself (650), Berkson (875, 2463), and others have pointed out the grave danger of bias if the control group is not selected in such a manner as to represent (in respect to smoking habits) the general population which includes the lung cancer patients.

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Proponents of the tobacco theory concede that subsequent events have proved this criticism is well founded, but claim that the direction of bias in most studies turned out to yield an underestimate of the degree of association between cigarette smoking and cancer of the lung. The reason was that in most of the retrospective studies the control group consisted of patients with diseases other than lung cancer. The choice of such a control group was tantamount to assuming that there was no association between smoking and diseases which result in hospitalization of the control patients. They (3409) now claim that this was an incorrect assumption since the prospective studies (153, 2534-A, 2534-B, 628-B, 918-D, 2761) have indicated an association between smoking and a number of diseases, e.g., coronary artery disease, thromboangiitis obliterans, and cancer of the buccal cavity. Indeed, one report (153, 2534-A, 2534-B) found an association with a plethora of other cancers not related to the respiratory system.

Hammond and Horn (C.A. Bull. Cancer Prog., 2(3), 97-98 (1952)) also criticized the retrospective method on the ground that:

"\* \* \* although it is easy to define the lung-cancer group, it is very difficult to define the control group. After all, who belongs in a sample of 'people-without-lung-cancer?' We have more than 150 million such

people in the United States to choose from. In most studies, hospital or clinic patients with other diagnoses have been used -- in the most carefully controlled studies the lung cancer and the control groups have been matched with respect to sex and age. There are, however, many selective factors representing differences in the two groups that are practically impossible to control, because they are cultural factors related to the smoking habits of the group.

Furthermore, when these cases are subdivided into several small subgroups, the proportions used to evaluate the result are based on small numbers in the denominators of the fractions. As a result, it takes relatively little bias on the part of the interviewer or on the part of the patient who may have been told by his physician that smoking has caused his symptoms to produce large fluctuations in the data."

Doll and Hill in their retrospective study (102, 103) in 1952, recognizing the possibility of bias in a control group selected from hospital patients, obtained an additional control group by ascertaining the smoking habits of the general population in a random sample of the several areas in which their hospitals were located. The largest percentage of smokers (particularly heavy smokers) was found in the lung cancer group, the smallest percentage of smokers was found in the general population sample, and an intermediate percentage of smokers was found in the hospital-control group. Similarly, in a recent study of lung cancer in women conducted by Haenszel, Shimkin and Mantel (3130), the

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percentage of smokers in the hospital population was greater than that of the general population.

Berkson (875, 2463) in 1958 pointed out that criticisms in regard to selection bias in the retrospective studies are also applicable to the earlier findings in a prospective study. He argued as follows: Suppose, that in selecting subjects for a prospective study, sick smokers are over-represented in relation to well smokers and/or well smokers are over-represented in relation to sick nonsmokers. In this event, during the earlier period, after selection, the death rate of the smokers in the study would be higher than the death rate of the nonsmokers in the study, even if death rates were unrelated to smoking habits of the general population. If smoking is unrelated to death from lung cancer (or other causes), the death rate of the smokers would tend to equalize with that of the nonsmokers as the study progressed in time. Thus, the bias would diminish with time, and a relationship due to such bias would disappear.

However, Hammond and Horn (153, 2534-A, 2534-B), recognizing this possible difficulty, had endeavored to exclude from their study all persons who were obviously ill at the time of selection. As expected, the total death rate of the study population was low and very few

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deaths from cancer of the lung occurred during the initial eight months after the selection period. The total death rate, and particularly the death rate from cancer of the lung, rose considerably in the subsequent three years of the study. What is more important, the observed association between cigarette smoking and cancer of the lung was considerably higher in the latter part of the study than in the earlier part, and the association between cigarette smoking and total death rates was also somewhat greater in the latter part of the study. This is relied upon to show that the original bias in the selection of the subjects was slight; that it yielded an underestimate of the degree of association between smoking and death rates at the beginning of the study; and that, in time, the bias lost its significance.

The subjects for the Hammond and Horn prospective study (153, 2534-A, 2534-B) were selected by volunteer workers of the American Cancer Society with specific instructions on how the selection should be done. In 1956 Mainland and Herrera (1253) suggested that the volunteer workers may have introduced a bias in the way they selected the subjects. According to Cornfield et al. (3409), this bias, if it existed, would also be eliminated by the passage of time.

Neyman [Science, 122, 401-406 (1956)] pointed out

that a study based on a survey of a population at some given instant of time may yield misleading results. Suppose that a study is made on a day when all patients with cancer of the lung and a group of people without cancer of the lung are questioned about their smoking habits. If smokers with cancer of the lung lived longer than nonsmokers with cancer of the lung, there would be a higher proportion of smokers in the lung-cancer group than in the control group - this would follow without questioning the proposition on which the model is based. However, only two of the retrospective studies were conducted in a way approximating an instantaneous procedure, so that this does not apply to most of the studies. Furthermore, this difficulty was completely avoided in the three prospective studies conducted by Hammond and Horn, Doll and Hill and Dorn.

The particular problem noted by Berkson (875, 2463) in respect of selection bias was not encountered in the prospective study of Doll and Hill (628-B, 918-D), who observed the death rates of all physicians in Great Britain (non-responders as well as responders to the smoking questionnaire). Similarly the prospective study of Dorn (2761) had a defined population: veterans holding insurance policies; thus, non-responders could be observed as well as responders. These two studies also showed

that higher mortality from cancer of the lung among smokers was more evident during the later period than in the earlier period of observation, which indicates that any bias resulting from the selection was worked out in the course of time.

With respect to Berkson's criticism of the prospective studies of Doll and Hill (628-B) and Hammond and Horn (153), Korteweg (1242) criticized Berkson's theory as follows:

"Berkson points out, quite rightly, that, inasmuch as the death rates found by Hammond and Horn .... are lower than the death rates of the official mortality statistics, their material should be considered as 'selected' with respect to the entire American population.

Berkson also points out, quite rightly, that, in research into an association between smoking and lung cancer, due attention should be given to the psychological reluctance of smokers to cooperate ....

.... starting from similar assumptions and using a similar model, .... we found: (1) that because of the action of this selection, as caused by the tendency for many smokers to eliminate themselves, only a small part of the excess death rates for lung cancer and for coronary disease in smokers can be explained as being spurious; therefore, the major part of this excess is not due to this selection but to one or more other factors; (2) that this selection gives a plausible explanation for the excess in death rates for smokers for 'other diseases' and 'other cancers,' so that excess in death rates in these diseases should be considered as being wholly artificial; (3) that the spurious excess of death rates for smokers, as caused by this selection, is

proportional to the quantity of cigarette smoked; (4) that, when in the reference population a percentage of smokers is assumed as being 80 this selection causes a decrease of this percentage to 72.5, so that part of the 'shortage' of smokers, found in Hammond and Horn's investigation can be explained by the action of this selection.

If our opinion is correct, it follows that Hammond and Horn's death rates entitle us to believe in a large and true excess of death rates with smoking and lung cancer and in coronary disease, whereas the excess they recorded in 'other cancers' and in 'other diseases' should be regarded as spurious.

To conclude: two objections which are often raised against Hammond and Horn's results: (1) the excess in death rates among smokers from causes of death with which an association with smoking would seem very improbable, and (2) the small percentage of cigarette smokers, may quite plausibly be explained by the psychological reluctance of smokers to enter this kind of an investigation.

If we accept this psychological reluctance as a fact, Berkson's suggestion does not undermine - on the contrary it supports - our belief that cigarette smoking is causally related to lung cancer, and perhaps to coronary disease."

In 1954 Kreyberg (241), in discussing the statistical studies relating lung cancer to cigarette smoking, noted

"....even if correspondence is established between the patient group and the control material with regard to such factors as age and sex composition, distribution of broad occupational groups and place of residence, which may influence smoking habits and/or lung cancer frequency, and a large number of factors clearly may be considered irrelevant, a field of uncertainty of considerable extent still remains."

b. Accuracy of Information (Diagnosis)

Berkson (875, 2463) in 1955 and 1958 remarked that the two major variables considered in these statistical studies, the diagnosis of disease and the ascertainment of smoking habits, are both subject to considerable error.

The accuracy of diagnosis is not a major problem in retrospective studies because the investigator can restrict his studies to those patients whose diagnosis of lung cancer has been thoroughly confirmed. This feature has been taken into consideration in several of the retrospective studies. It is more of a problem in prospective studies since all deaths that occur must be included, and certainly some of the diagnoses will be uncertain. Nevertheless the importance of errors of diagnosis is lessened by the fact that in all three prospective studies (628-B, 918-D; 2761; 153, 2534-A, 2534-B) the total death rate was found to be higher in cigarette smokers than in nonsmokers and found to increase with the amount of cigarette smoking. In other words, if some of the excess deaths associated with cigarette smoking and ascribed to cancer of the lung were actually due to some other disease, then it means that: (a) the association between cigarette smoking and cancer of the lung was somewhat overestimated, but (b) the association between cigarette smoking and some other

disease was somewhat underestimated. The reverse would be true if some of the excess deaths associated with cigarette smoking and ascribed to diseases other than lung cancer were actually due to lung cancer. It is obvious, however, that errors of diagnosis remain significant in regard to the relationship between smoking and lung cancer. Moreover, one might argue that an association between smoking and death from a large number of causes suggests validity in the theory that there are emotional and other selected characteristics predisposing certain individuals to both smoking and various diseases. (See Lilienfeld (3485), discussed hereinafter in the section on constitutional hypothesis).

It should be noted here that Hammond and Horn (153, 2534-A, 2534-B), aware of the dangers of erroneous diagnosis, divided their group into lung cancer microscopically confirmed and those otherwise diagnosed and found that the association with cigarette smoking was greater for the group of patients with a microscopic diagnosis of lung cancer than for the group of patients with both microscopic and less convincing evidence of lung cancer. This suggests that inaccuracies in all diagnosis resulted somewhat in an underestimate of the degree of association between smoking and cancer of the lung.

IV-B-61

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The study on physicians, by Doll and Hill (628-B, 918-D), in which presumably the clinical and pathological evidence of the cause of death would be somewhat more than in the general population considered by Hammond and Horn (2534-A, 2534-B) and by Dorn (2761), yielded risk ratios for smoking and lung cancer almost identical to those found by Hammond and Horn.

Accuracy of Information (Smoking Habits)

In regard to information about smoking habits, Finkner and co-workers (2519) have made a thorough study of the accuracy of replies to questionnaires on smoking habits. Their results, published in 1957, indicate that replies are not completely accurate but that most of the errors are relatively minor, i.e., very few heavy smokers are classified as light smokers. It should be noted, however, that the study conducted by Finkner et al. did not involve very many subjects. Random and independent errors simply tend to diminish the apparent degree of association between two variables.

A national survey of smoking habits in the United States conducted by Haenszel, Shimkin, and Miller (1156) yielded results on tobacco consumption in the male and female population that were consistent with figures on tobacco production taxation.

On two separate occasions several years apart,



both Hammond and Horn (2534-A, 2534-B) and Dorn (2761) questioned a proportion of their subjects as to their smoking habits. The results obtained in both instances indicated, they claimed, close reproducibility in the answers obtained.

Hammond (650) and other workers, Macdonald (2084) for example, have questioned the reliability of the retrospective method on the grounds that the illness may bias the responses given by the patient or his family when they are questioned about smoking habits, and that knowledge of the diagnosis may bias the interviewer. This possible difficulty was minimized in several of the 21 retrospective studies on smoking in relation to cancer of the lung. For example, in the study conducted by Levin (258), all patients admitted to a hospital during the course of several years were questioned about their smoking habits prior to diagnosis. Only a small proportion later turned out to have lung cancer, though many had lung disease symptoms or lung diseases other than cancer of the lung.

Doll and Hill (628-B, 918-D) also showed that patients whose diagnosis of cancer of the lung was subsequently established to be erroneous had smoking histories characteristic of the control rather than of the lung-cancer group. Furthermore, a larger percentage

of cigarette smokers have been found among patients with epidermoid or squamous carcinoma of the lungs than among patients with adenocarcinoma of the lungs (670, 1300, 3130). On the other hand, Hammond and Horn (2534-A, 2534-B) claimed to have detected a gradation in adenocarcinoma incidence with amount smoked although this gradation was not as pronounced as in the case of the squamous-cell carcinoma. These findings could hardly have resulted from bias either on the part of the patient or on the part of the interviewer.

IV-B-64

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c. Other Noteworthy Criticisms Of The Statistical Studies

Arkin (866-B) has criticized the statistical studies of Hammond and Horn (153, 2534-A, 2534-B) because of these authors' failure to obtain data on the subjects involved other than their smoking habits. The validity of this criticism is dramatically demonstrated by the questionnaire used by Hammond and Horn (153), a copy of which is inserted following this page. Arkin said:

"As to ruling out other possible causes which may be associated with both death rates and smoking habits, Hammond and Horn must, from the statistician's viewpoint, be charged with serious neglect in failing to secure data on the respondent's characteristics (physical, social, or occupational) other than location, age and smoking habits for the entire sample. The published questionnaire contains no evidence of questions relating to these other characteristics."

Little (2082) and Macdonald (2084), and others, have also criticized the studies of cigarette-lung-cancer relationship on the grounds that only smoking habits were really investigated, and that numerous other possible variables were not considered. Occasionally where other variables have been given attention, their importance has been de-emphasized by followers of the statistical studies. For example: atmospheric pollution.

These criticisms may seem especially appropriate in view of the fact, accepted by even the most enthusiastic advocate, that no single etiologic factor has been proposed for any neoplastic disease. The criticism may also be valid in relation to any one of the retrospective and prospective studies. However, as pointed out by Cornfield et al. (3409), quite a number of other variables have been specifically investigated or can be inferentially derived. Of course, all studies considered the basic factors of age and sex; some dealt with geographic distribution (1104-A), occupation (615-A), urban or rural residents (1104-A), marital and parous status (3130), and some other habits such as coffee consumption (3130).

Berkson (875, 2463) has criticized the prospective studies of Hammond and Horn (153, 2534-A, 2534-B) and Doll and Hill (628-B, 918-D) as to whether the association between lung cancer and cigarette smoking noted in these studies can rightfully be considered a cause-and-effect relationship. This has been a criticism levelled at the statistical studies by a great many commentators. For instance, some of the more prominent authorities have expressed themselves as follows:

IV-B-66

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Gilliam (780-A):

"Whether or not this [the statistical association] is a general fact cannot be determined from one case history study, but if true, lends support to but by no means proves, the contention that the association between cigarettes and lung cancer may be an indirect one.

"What, finally, is required for establishing 'proof' of the cigaret hypothesis; or on the other hand, upon what grounds may it be rejected entirely? 'Proof' in the mathematical sense is unattainable in dealing with medical phenomena."

Greene (2075-A):

"An example may be cited here as illustrative of the possibility that a predilection for lung cancer and an abnormal desire for cigarette smoking may be part and parcel of the same constitutional habitus rather than a cause and effect sequence .... The point to be made is that if cigarette smoke and lung cancer have any relationship it may well be of this variety and without any significance whatsoever from the point of view of causation."

Haenszel and Shimkin (954-A):

"It must be accepted that an association between smoking and an increased risk of lung cancer has been observed repeatedly. The inference from this association of a causal relationship, however, has been challenged."

Deibert (1576) criticized the retrospective studies of Wynder and Graham (475) and Levin et al. (258) on the classification of the smokers, re pipe, cigar or cigarette smoker. In other words, he found fault with the fact that some studies included all

types of smoking (pipe, cigar and cigarette, e.g. Wynder and Graham (474)), while another study (258) showed that only cigarette smoking is statistically related to lung cancer. A similar criticism, made by Rigdon et al. (976, 1911-A), raises the question as to whether it is proper to convert cigar and pipe smoking into cigarette smoking on the basis of an arbitrary measure, such as so many cigars being treated as the equivalent of so many cigarettes, as the studies of Doll and Hill (102, 103) have done.

Doll and Hill (102), themselves the authors of a retrospective study, noted that the retrospective studies of Muller (296) and Schrek et al. (388) were small scale studies and hence inconclusive. In their 1950 study, Wynder and Graham (474) reviewed earlier studies and gave them short shrift, primarily on the basis that they involved so few persons as not to be reliable. The same criticism can be directed to statistical studies on female lung cancers as related to smoking.

Gilliam (780-A) criticized the retrospective studies conducted by Muller (296), Wynder and Graham (474), Doll and Hill (102, 103), Schrek et al. (388) and Levin et al. (258) on the basis that

\*\*\*the case history (retrospective) method of eliciting an association such as this

is an indirect method which is very sensitive to sampling factors which determine representativeness of study persons selected for interview. The absolute security of conclusions which may justifiably be drawn from case history studies \*\*\*\* may be open to question in spite of repetition of findings."

He views the main distinction between the retrospective and prospective methods of measuring risk as being in the point of departure of the study. In the former, it is "with a series of cases and controls with all of the selective factors involved", and in the latter, it is a group of people without initial regard for the disease under study. Even the prospective method is prospective, as he points out, only in the sense of future disease experience - it is still retrospective in reference to attributes of the population: present and past smoking history.

Numerous other retrospective studies were criticized indirectly by reference to those studies quoted by Cutler (777). These studies are listed in Tables III and IV. Hammond (650-D) criticized all retrospective studies published up to 1954. Hammond and Horn (956-B) criticized specifically the statistical studies of Schrek et al. (388), Levin et al. (258), Wynder and Graham (474) and Doll and Hill (102, 103) because these studies disagreed

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".... so markedly in their measurement in the size of that relationship as to preclude the possibility that random variability is responsible for the differences. The apparent importance of tobacco varies in these studies from relative unimportance, of academic interest only, to an appearance of crucial importance and of major clinical interest."

Hilding (965) criticized the statistical studies in general because

".... the smoker's statement of the number of cigarettes that he smokes is not a reliable measure of the amount of smoke taken into his mouth."

Hueper (657-E) criticized the retrospective statistical studies because in these studies the percentage range for nonsmokers varied from 1.3 to 14.6 percent for the various lung cancer groups, and from 8.8 to 30.5 percent for the control groups. Another criticism offered by Hueper (970-D) was that there was no positive statistical association between lung cancer and cigarette cough although this latter symptom is clinically characteristic of the chronic chain smoker. Hueper (1707-C) also noted

"apart from the fact that some of the data used in these calculations are of dubious scientific value, the markedly irregular epidemiologic pattern of lung cancer for various regions and population groups associated with exposures to industry-related air pollutants of widely different types and degrees practically excludes the possibility that one single factor is involved...."

IV-B-70

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Mills and Mills-Porter (287) took to task Schrek et al. (388) because of their use of hospitalized tumor patients as their control group instead of a normal population cross-section. In another study (288), they commented on the retrospective studies of Doll and Hill (102, 103) and Wynder and Graham (474) as follows:

".... it would seem that the results of previously published investigations of the effects of tobacco smoke may have been more significant had they been obtained with a valid control cross-section of the total population...."

In discussing smoking and lung cancer, Passey (690) stated:

".... we cannot assume that, because there is a correlation between the increase in smoking and the increase in lung cancer, there is necessarily a connection between the two. It is easy to call to mind other close statistical correlations ...."

Rienhoff stated in 1955 that the statistical case against the cigarette is inaccurate and obscure and contradictory. In respect of the statistical studies, Rigdon and Kirchhoff (1413) noted in 1952 that

".... the statistical data presented by some investigators relative to cigarette smoking are impressive; however, there is such a wide variation in control samples that, in our opinion, additional sampling is needed to warrant their conclusions. There is no significant correlation between

the amount of tobacco consumed and the death rate for cancer of the lung in the United States. There is, however, a significant correlation in the United States between the population to physician ratio and the population to bed ratio and the number of reported deaths from cancer of the lung...."

In 1955, Rigdon et al. (698) revealed that the number of deaths from cancer of the lung in each county was related to the number of doctors and the number of hospital beds in the county. Better diagnosis, therefore, according to them, was a significant factor in the increase in the frequency of cancer of the lung.

Sadowsky et al. (378) disclosed several inconsistencies in their own study of the statistical association between smoking and carcinoma of the lung:

".... it is assumed, in conformity with experience with carcinogens in experimental animals, that if smoking is cancer-producing, that indulged in just prior to disease is less important than that indulged in at a more remote time....

"The average ages at diagnosis were also calculated for each class of illness according to quantity smoked. If smoking were etiologically related to cancer it might be expected a priori that those smoking the largest amounts could develop illness at a younger age than those smoking smaller amounts .... No regular relationship was discernible between average age and diagnosis and quantities of tobacco of various types smoked.... These data also provide no evidence that age at on-set of disease is influenced by the quantities of cigarettes smoked. While the

lack of such evidence may be due to an insufficient number of cases, no suggestion of an increased average age at onset with decrease in cigarettes used, was evident. This point needs testing in other series since one might expect such a correlation if cigarettes were of etiological significance."

"Despite the absence of definite proof in one or the other direction, the assumption has generally been made that the incidence has increased, and this has been considered as a clue in the search for a related environmental agent. Many factors in man's environment have changed in the past 50 years, and several of these pertain directly to the lung. The atmosphere has become polluted with the exhaust gases of industry and the automobile; tobacco smoking has become a universal habit; and x-ray examination for the early detection of tuberculosis has become a standard procedure to which many individuals have been subjected at frequent intervals. There are many other factors, any one of which shows an increase in prevalence comparable to that believed to obtain in lung cancer; but for reasons that appear more subjective than objective, major attention has been directed toward smoking."

IV-B-73

2025018198

d. Other Factors Not Studied, or if Studied,  
not Sufficiently Emphasized

(i) Urban-Rural

See "Environmental Factors in Lung Causation".

(ii) Male-Female Ratio

In 1954, Hueper (657-F) criticized the retrospective statistical studies on the basis of the appreciable differences in the sex distribution of lung cancers reported at different times, from different regions and by different investigators. The male to female sex ratio fluctuates from 2:1 to 20:1. The uniformly observed prevalence of lung cancer among males has, in general, become in recent years even more pronounced than in former decades. This observation, he believes, strongly militates against the predominant causal role of cigarette smoking in the production of lung cancer, because experience with occupational cancer has taught that, given the same type of carcinogenic exposure for both sexes together with an increasing equalization of intensity of exposure, a narrowing of the incidence gap between the two sexes occurs. Hueper's thesis is based, of course, upon the assumption (which he makes) that the cigarette habit has made much greater strides among

2025018199

women than men.

The sex disparity in lung cancer mortality has also been cited by Fisher (2210-A) and Macdonald (2084) as reasonable grounds for discarding the cigarette smoking-lung cancer hypothesis.

According to Cornfield et al. (3409) persons advocating this line of argument have minimized sex differences in smoking habits to a degree not supported by the available facts. They quote the survey of Haenszel and Shimkin (1156) (on smoking habits in a cross-section of the U. S. population) which demonstrates that men, on the average, have been smoking for longer periods than women. The sex differences in tobacco use were especially pronounced at ages over 55, when most lung cancer deaths occur; 0.6 percent of U. S. females in this age group were reported as current users of more than one pack of cigarettes per day compared to 6.9 percent of U. S. males. Comparable British data (2690-A) also revealed a much lower tobacco consumption among the female population, particularly for the years prior to World War II.

Indeed, Cornfield et al. (3409) interpret the present data contrasting the experience by sex as supporting the cigarette smoking-lung cancer hypo-

thesis rather than discrediting it. They rely on a paper published by Haenszel and Shimkin (954-A) in 1958 which reported the results of a study of the smoking histories of 45,000 persons 18 years old and over in an effort to determine whether the epidemiology of lung cancer is compatible with smoking patterns in the United States. By taking into account the observed differences in smoking habits between males and females they were able to reduce the observed five-fold excess lung cancer mortality among males to the 40 percent excess mortality which prevails for many other causes of death. Cornfield et al. (3409) also noted that the estimated death rates for female nonsmokers agreed closely with the death rates derived from retrospective studies on male nonsmokers as described in a 1958 paper by Haenszel, Shimkin and Mantel (3130).

With respect to the sex disparity, Nelson (1847) noted:

"Insofar as the sex differences in lung cancer are concerned, if one assumes that the sexes are equally susceptible, then smoking perhaps more readily fits available data than does air pollution on the basis that the frequency of smoking among women has only in recent years approached that among men, whereas women would be presumably equally exposed to general pollutants. If this is the explanation, the present dis-

IV-B-76

2025018201

parity should disappear in the future. On the other hand, the initial assumption as to equal susceptibility of the sexes may be quite wrong; in this case the present disparity would be expected to persist."

Nelson's assumption that women are as exposed as men to air pollutants is at variance with Kotin's opinion on this subject (982).

(iii) Constitutional Hypothesis

In 1959 Cornfield et al. (3409) summarized the three possible interpretations of the observed association of lung cancer and cigarette smoking as follows:

- (1) Cigarette smoking "causes" lung cancer either through the direct carcinogenic action of cigarette smoke on human bronchial epithelium or by a more indirect mode of action such as making the individual susceptible to some other specific carcinogenic agent in the environment. This is designated as the causal hypothesis.
- (2) Lung cancer "causes" cigarette smoking perhaps because a precancerous condition sets up a process which leads to a craving for tobacco smoke.
- (3) Cigarette smoking and lung cancer both

have a common cause, usually specified as a special constitutional make-up, perhaps genetic in origin, which predisposes certain individuals both to lung cancer and to cigarette smoking. This is designated as the constitutional hypothesis.

Parenthetically, we think one should bear in mind that the three possible interpretations advanced by Cornfield et al. are valid only if one accepts the association as an invariable one. The very fact that nonsmokers contract the disease utterly destroys hypothesis number one, for this fact means that there must be some other, unidentified additional explanation for the association.

They noted that Fisher (2521) had advanced hypothesis number two, apparently for the sake of logical completeness. They were not certain whether Fisher meant this hypothesis to be considered as a serious possibility.

The constitutional hypothesis may be further subdivided into at least two important categories; namely, the genetic constitutional hypothesis and the hormonal hypothesis.

IV-B-78

2025018203



With respect to the genetic constitutional hypothesis, Little (2082) in 1957 noted that there was a great difference in the reaction of individuals of the same age, sex and environment to the development of lung cancer. Investigations on the probability of lung cancer have shown that a great percentage of excessively heavy smokers do not develop cancer of the lung. Little posed the question: "Why does a small minority develop it (lung cancer) while the great majority does not?" Preliminary studies have indicated that there are significant differences in the physiological, psychological and emotional make-up of the types of person involved. Thus, the taking up of excessive smoking, according to Little, may be indicative of such differences and not necessarily the cause of them.

Macdonald (2084) in 1957 also noted the genetic constitutional hypothesis and provided a rather striking example of its application with respect to skin cancer:

"The genetic influence of importance is the character of the individual's skin; the person with thin, delicate skin usually seen in blondes and redheads is extremely sensitive to the environmental agent, which in this instance is sunshine, or at least the ultraviolet fraction of solar radiation. Another fact of importance is that people without sensitive skin structure

2025018204

if exposed over a long period of years to excessive amounts of sunshine have about the same hazard of developing skin cancer as does the person with 'redhead skin' who limits his exposure. This will emphasize another point, that an excessive amount of a potentially cancer producing substance over a long period of time may make the individual who otherwise would have been resistant become as susceptible as a sensitive individual. In other words, three separate considerations are involved; sensitivity of the individual, exposure to the possible cancer producing substance, and the duration of exposure.... Thus we are aware of factors of individual inherited sensitivity and of the most important single environmental influence which combine to create the hazard of skin cancer, yet we do not have any understanding of the trigger mechanism which sets off actual skin cancer in one person."

Macdonald suggested that this genetic constitutional factor is probably operative in the lung cancer case as well.

Arkin (866-B) has stated in support of a constitutional hypothesis:

"There is little doubt, however, that cigarette smoking is associated with higher death rates, but it is most unlikely that it is a cause rather than a symptom or indication of the type of people with higher death rates."

Wynder et al., at a symposium held in 1953 at New York Hospital, Cornell University Medical Center, also pointed out:

".... that not every person who smokes develops cancer of the lung. This may be the result of individual differences in predisposition."

IV-B-80

2025018205

Gsell (1668) also considered that constitutional factors were important and stated:

"..... Although the various statistical and experimental results show clearly a significant correlation between lung cancer and inhaled poisons, including tobacco smoke, carcinogenesis depends also on a constitutional factor (of which progressive age is one).

Only a combination of constitutional and exogenous factors will produce an immediate danger of cancer development....."

Similar sentiments have been expressed by Haenszel (954-B):

"..... Constitutional susceptibility might also be considered. If some persons have a predisposition to attacks of lung tissue by some morbid process, the rise in lung cancer might be due to the suppression of 'competitive' respiratory causes..... There is the possibility of the association of smoking with other physical, psychological and emotional factors which may be engendered by the processes influencing persons to take up smoking."

and by Hueper (1706-D):

"..... The degree of susceptibility to a carcinogen is also influenced by inherited, congenital, or acquired constitutional factors ....."

Levin et al. (671, 994, 1382) stated on several occasions that constitutional factors may be involved, e.g.:

"..... Such factors may be those of inherent susceptibility, exposure to other chemicals ....."  
 "..... That susceptibility plays a major role is strongly suggested by the fact that a large proportion of heavy smokers apparently do not develop lung cancer....." (1382)

"The fact that cigarette smokers suffer an appreciable increased risk of lung cancer does not \*\*\* amount to proof that this increased risk is caused by cigarette smoking. It could also be due to the fact that cigarette smoking was in turn associated with some other factor or factors which were carcinogenic. \*\*\*"

It does not indicate that it is the sole causative factor or even that it is operative in the absence of other factors, such as susceptibility \* \* \* " (671)

But in a recent article Levin et al. (994) do not favor the constitutional hypothesis:

".....The hypothesis has been advanced that lung cancer occurs more often in smokers because people who smoke also have some constitutional or hormonal abnormalities that increases their susceptibility to lung cancer. Lung cancer in man has not been linked with any constitutional or hormonal abnormalities, nor has it been shown that cigarette smokers have any inherent constitutional or hormonal abnormalities. However, even if this were to be shown, it would not necessarily exclude cigarette smoking as a causative factor that enhances the effect of these or other causative factors....."

Peacock (1046-D), Nelson (1847) and Watson and Conte (719-A) have discussed inherent susceptibility of the individual in relation to lung cancer and consider that it is an important factor.

With respect to the hormonal hypothesis, Cameron (3399), one of the more vigorous critics (897) of the Tobacco Industry and the Tobacco Industry Research Committee, stated

"The question uppermost in the minds of scientists at the moment is whether the well-established and generally accepted statistical association between cigarette smoking and cancer of the lung is one of cause and effect, or whether it is incidental. It is possible that the tendency to smoke heavily and the tendency to get lung cancer are both the result of a common and yet unidentified factor or cause. One such influence might be a distinctive type of hormone balance. It is known that hormones seem to be involved in the development of certain kinds of cancer, and it is conceivable, though far from proved, that hormone stimulation may be responsible for a high pace of living, carrying with it an intense desire to smoke."

With respect to the constitutional and/or hormonal hypothesis, Greene (2075-A) in 1957 provided the following amusing, but very pertinent, example illustrating the possibility that a predilection for lung cancer and an abnormal desire for cigarette smoke may be part of the same constitutional habitus rather than a cause-and-effect sequence:

"..... It was noted long ago that the front row in burlesque houses was occupied predominantly by bald-headed men. In fact, such a row became known as the bald-headed row. It might be assumed from this on statistical evidence that the continued close observation of chorus girls in tights caused loss of hair from the top of the head and thus one could construct a nice cause and effect sequence relating the two. However, subsequent investigation has shown that in effect bald headedness and the desire to see chorus girls at close range are part of the same constitutional diathesis. Both are due to an excess of the male hormone testosterone. On the one hand this hormone in abundance brings about excessive virility and on the other causes the hair on top of the head to fall out..... if cigarette smoke and lung cancer have any

2025018208

relationship it may well be of this variety and without any significance whatsoever from the point of view of causation."

Kreyberg (985) also considered the possibility that hormonal factors might be involved in lung cancer development. He remarked:

"..... This very great difference.....makes it difficult to ascribe the whole sex difference in the occurrence of group I tumors [group I tumors include squamous-cell carcinomas, large- and small-cell carcinomas] to external factors alone. A biological sex difference, architectural and/or biochemical, influencing the response of the lungs to some, or all, of the principles causing lung cancer cannot be excluded."

The constitutional hypothesis is rejected by the proponents of the causal hypothesis on the following basis, as outlined by Cornfield et al. (3409):

"..... Nothing short of a series of independently conducted, controlled, experiments on human subjects, continued for 30-60 years, could provide a clear-cut and unequivocal choice between them (the causal and constitutional hypotheses)."

The authors argue that

"..... evidence, in addition to that associating an increased mortality from lung cancer with cigarette smoking, is entirely consistent with the causal hypothesis but inconsistent, in many respects, with the constitutional hypothesis, so that even in the absence of controlled experimentation on human beings the weight of the evidence is for the one and against the other.

The difficulties with the constitutional hypothesis include the following considerations:

- (a) changes in lung-cancer mortality over the last half century;

- (b) the carcinogenicity of tobacco tars for experimental animals;
- (c) the existence of a large effect from pipe and cigar tobacco on cancer of the buccal cavity and larynx but not on cancer of the lung;
- (d) the reduced lung-cancer mortality among discontinued smokers.

No one of these considerations is perhaps sufficient by itself to counter the constitutional hypothesis ad hoc modification of which can accommodate each additional piece of evidence. A point is reached, however, when a continuously modified hypothesis becomes difficult to entertain seriously."

With respect to the constitutional hypothesis, Hueper (970) in 1956 noted

"..... Although some occupational, medicinal and experimental observations suggest that pulmonary carcinogenesis may ensue after a non-respiratory contact with carcinogens, there exists no valid evidence incriminating hereditary or endogenous factors as primary causal agents of human lung cancer."

And Kotin (982) in the same year stated:

"..... There is no convincing evidence that an intrinsic biological change might be responsible for the emergence of nonoccupational lung cancer from the status of a medical curiosity at the beginning of the century to a position of major importance at mid-century. In the absence of such data an exogenous source of the carcinogenic agents must be postulated."

In a very recent paper (published in 1959) Lillienfeld (3485) cited one of the objections of Berkson (2463) to the Hammond-Horn and Doll-Hill prospective studies, namely, that the observed association,

which is interpreted as a causal relationship by Hammond et al. and Doll et al., may be a result of "self-selection." Lillienfeld defines this self-selection as the unknown factors which cause an individual to smoke and hence are of etiological importance for lung cancer. In an effort to determine whether there is such a self-selection factor he interviewed a total of 4,456 adults residing in Buffalo and Kenmore, N. Y. as to their emotional status and smoking habits.

One possible interpretation of the results of this study is that cigarette smoking may be a cause of the traits observed among smokers. Lillienfeld considered this unlikely, but possible. Another interpretation offered was that smoking and "neuroticism" both result from common underlying factors. Certain social factors may be interrelated with smoking habits, lung cancer and emotional status. Lillienfeld considers this as a form of the self-selection hypothesis, one step removed from the lung cancer-cigarette smoking association. He also considered this explanation as unlikely and difficult to test.

A third interpretation of the data would be that "neurotic" traits lead to the initiation of



the smoking habit. This was considered the most likely possibility and would indicate that smokers are a self-selected group.

Lilienfeld summarized his findings as follows:

"A self-selection explanation for the lung cancer-smoking relationship implies that emotional factors, within the context of the specific questions used in this study, are of etiological importance in lung cancer. In other words, cigarette smokers tend to develop more lung cancer than nonsmokers because they are more 'neurotic.' There is no evidence available with which such a possibility can be directly evaluated. For a direct test of this hypothesis, it would be necessary to select groups of smokers and nonsmokers among lung-cancer patients and groups of smokers and nonsmokers among controls, and subject them to a battery of psychological tests to determine whether or not emotional factors may be considered as being independently related to lung cancer. In view of the results of the present study, such an investigation would appear profitable.

The self-selection hypothesis can also be evaluated in terms of our knowledge of the epidemiology of lung cancer. First, the degree of association between emotional factors and cigarette smoking, as determined in the present study, does not appear to be sufficiently high to be a likely explanation of the marked association between cigarette smoking and lung cancer. To obtain some idea of the degree of association between emotional response and cigarette smoking, we thought it would be of interest to compute the risk of cigarette smoking for a 'neurotic' response relative to that of a 'nonneurotic' response, with a method suggested by Cornfield [J. Natl. Cancer Inst., 11, 1269-75 (1951)]. Since the responses were either in 3 or 4 categories,

computations were first carried out under the assumption that the most 'neurotic' category was a 'neurotic' response and the remainder 'nonneurotic.' Similar computations were then made under the assumption that the two most 'neurotic' categories were a 'neurotic' response and the remainder was 'nonneurotic.' The highest relative risk obtained was 2.6. Obviously this degree of association is not sufficient to account for the tenfold excess of lung-cancer mortality for cigarette smokers as compared to that of nonsmokers [153]. Admittedly, our method of measuring emotional status is rather crude and perhaps more refined methods might increase the degree of difference, but this cannot be assumed on the basis of the present data.

Another phenomenon would have to be explained to make the self-selection hypothesis tenable, namely, the marked increase in lung-cancer mortality during the past 2 to 3 decades [1594-A]. It would be necessary to assume that the frequency of 'neurotics' in the population has also increased during the same period. Although definitive evidence on this point is actually not available, such a marked change probably has not occurred. On the basis of present evidence, the fact that cigarette smokers are more 'neurotic' than nonsmokers does not detract from the hypothesis that cigarette smoking is an etiological factor in lung cancer.

It is possible that the 'neurotic' traits of cigarette smokers may be an explanation, in whole or in part, of the association between cigarette smoking and other diseases, such as coronary artery disease and peptic ulcer, each of which may be related in some manner to psychological factors. For instance, the association between these diseases and cigarette smoking is not as strong as the association between cigarette smoking and lung cancer. Also, the increase of coronary artery disease mortality has not been as great as that of lung cancer during the past 2 to 3 decades [1247-A]. With respect to peptic ulcer, it is thought that, in Britain, the incidence of gastric ulcer has diminished, whereas

that of duodenal ulcer has increased, although in the latter the statistical association with cigarette smoking is less [2503-A]. Thus, self-selection may be a reasonable explanation for the association of peptic ulcer and coronary disease with cigarette smoking. Studies of the relationship of emotional factors to coronary disease and peptic ulcer among nonsmokers should be carried out to shed further light on such possibilities."

In 1958 Heath (2537) published the observed differences in the smoking habits of 252 Harvard graduates (61 nonsmokers, 95 moderate smokers, 96 smokers of over a pack a day) based upon a fairly detailed personal history over 15 years. Smokers were found to be more energetic, more "interesting" and less stable than nonsmokers who tended to be dependable but "colorless". Nonsmokers tended to specialize and make careers in science and engineering. Smokers preferred majors in the humanities and business careers. Cigarette smokers tended to breathe more rapidly and have slower reflexes than nonsmokers. Heavy smokers tended to drink more coffee and alcohol and to eat more.

About the same time McArthur et al. (2591) published their observations on the psychology of smoking using the same sample as Heath. Nonsmokers tended to be persons of lower middle class origin, who were introverts and serious-minded. Very heavy

IV-B-89

2025018214

smokers tended to be impulsive and disposed to violence. Groups with the ability to stop smoking contained a smaller percentage of bottle babies.

Friberg, et al. (3618) (in 1959) and Fisher (2960, 3116) (in 1958) have recently shown in two separate studies of monozygotic (one-egg) and dizygotic (two-egg) twins that constitutional factors may influence smoking habits. The Friberg study involved 59 pairs of adult monozygotic and 59 pairs of adult dizygotic twins. The studies reported by Fisher comprised 51 pairs of adult monozygotic male twins and 31 pairs of adult dizygotic male twins (2960).

The data from these studies showed that the pairs of monozygotic twins are more alike in their smoking habits; whereas, the pairs of dizygotic twins are less alike in respect of smoking habits. Tables VI and VII summarize these data.

TABLE VI  
SMOKING HABITS OF TWINS (A-REGULAR SMOKERS, B-SPORADIC SMOKERS, C-FORMER SMOKERS, D-OTHER NONSMOKERS) (3618)

<u>Monozygotic Pairs</u>					<u>Dizygotic Pairs</u>				
<u>Twin</u>	<u>Twin II</u>				<u>Twin</u>	<u>Twin II</u>			
<u>I</u>	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>	<u>I</u>	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
A	15 <sup>a</sup>				A	15 <sup>a</sup>			
B	3 <sup>b</sup>	3 <sup>a</sup>			B	0 <sup>b</sup>	0 <sup>a</sup>		
C	3 <sup>b</sup>	0 <sup>b</sup>	1 <sup>a</sup>		C	7 <sup>b</sup>	0 <sup>b</sup>	0 <sup>a</sup>	
D	4 <sup>b</sup>	1 <sup>b</sup>	3 <sup>b</sup>	26 <sup>a</sup>	D	11 <sup>b</sup>	2 <sup>b</sup>	5 <sup>b</sup>	19 <sup>a</sup>

<sup>a</sup> Number of pairs alike in each category

<sup>b</sup> Number of pairs not alike in each category

TABLE VII  
SMOKING HABITS<sup>a</sup>

	<u>Alike</u>	<u>Some Differences</u>	<u>Unlike</u>	<u>Total</u>
Monozygotic	33	6	12	51
Dizygotic	11	4	16	31

<sup>a</sup>Adapted from (2960)

Bleuler [Familial and Personal Background of Chronic Alcoholics, Etiology of Chronic Alcoholism, Thomas, Springfield (1955)] challenged the conclusions of Fisher on the basis that the environment of monozygotic twins may be more uniform than that of dizygotic twins but in a later study (3116) reported by Fisher, involving 27 pairs of female monozygotic twins who were reared apart, the results on smoking habits agreed very well with those in the study of the monozygotic group reared together (2960). These results are shown in Tables VIII and IX.

TABLE VIII  
SMOKING HABITS

	<u>Alike</u>	<u>Unlike</u>	<u>Total</u>
Monozygotic	44	9	53
Dizygotic	9	9	18

IV-B-91

2025018216

TABLE IXSMOKING HABITS OF MONOZYGOTIC TWINS

	<u>Alike</u>	<u>Unlike</u>	<u>Total</u>
Reared Separately	23	4	27
Reared Together	21	5	26

Unfortunately, the numbers of twin pairs are fairly small in these three studies and the results, while highly suggestive and probably valid, are open to the same criticisms that were leveled at several of the earlier retrospective statistical studies involving lung cancer and cigarette smoking, i.e., the studies were "careful but limited."

IV MULTIPLE CAUSES - IF TOBACCO SMOKE CAUSES  
LUNG CANCER, IS IT THE ONLY CAUSE?

Both before and after publication of the various statistical studies discussed previously, numerous authorities have suggested or asserted that there are causes other than cigarette smoking of the present high incidence of lung cancer. These include the following: Arkin (866-B), Brantigan (888), Breslow (50, 889), Campbell and Clemmesen (1538), Cohart (902-B), Cornfield et al. (3409), Daff et al. (92), Deibert (1576), Doll and Hill (102, 103, 628), Dorn (104-A), Eastcott (923), Eckardt (924), Finke (1628), Graham (948-D), Greene (2075-A), Gsell (1668), Haddow (1155-A), Haenszel (954-B), Hamilton et al. (2242), Hammond (650-D, 956-C), Hueper (657-G, 970, 970-C, 970-D, 1706-E, 1707-C), Kennaway (1369), Korteweg (668-A), Kotin and Hueper (786-A), Kotin et al. (237-A), Lacassagne (1245), Levin (671), Levin et al. (994), Little (2082), Macdonald (2309), Macdonald (2084), McConnell et al. (274), Mills (681, 681-A, 1831-A, 1831-C), Mittler and Nicholson (1392), Ochsner (308, 311-B), Paxon (1868), Peacock (1046-D), Rigdon (697, 698, 1413, 1911, 1911-A), Rosenblatt (701), Russ (376), Steele (1978), Stocks (415, 1103, 1104-A), Thomas (713) and Wynder (472-B, 2054).

It may be noted that the foregoing list includes numerous investigators who are also authors of statistical studies on the lung cancer-cigarette smoking relationship, namely, Breslow (615-A, cf. 50, 889), Doll and Hill (102, 103, 628, cf. 102, 103, 628-B, 918-D), Wynder and Graham (948-D, 472-D, 2054, cf. 473, 474), Gsell (1668, cf. 575), Haenszel (954-B, cf. 3130), Hammond (650-D, 956-C, cf. 153, 2534-A, 2534-B), Levin et al. (671, 994, cf. 258), McConnell et al. (274), Mills et al. (681, 681-A, 1831-A, 1831-C, cf. 287) and Stocks (415, 1103, cf. 1104-A).

Key quotations on the subject of multiple causation, from the work of some of the authors mentioned in the two preceding paragraphs, may be found in "Quotations from the Lung Cancer-Smoking and Laryngeal Cancer-Smoking Literature" by Rodgman collected in 1957. These writers do not claim for cigarette smoking a place as sole cause of the rapid rise in lung cancer incidence, and their position in this respect is still unchanged [see Cornfield et al. (3409)]. The following quotations may be taken as characteristic of their views on this aspect of the smoking controversy:

Lacassagne (1245):

"To sum up, it is necessary to consider what new

IV-B-94

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causative factors might play a part in epidermoid metaplasia of bronchial epithelium, giving origin to the cancers which are more and more commonly observed in the male. The most plausible factors may be classified under three headings: (1) increase in atmospheric pollution by certain dusts and products of combustion; (2) exposure at work to carcinogenic agents; (3) use of tobacco, and in particular of cigarettes..."

Wynder (1299-A):

"To consider smoking as a major cause of lung cancer does not mean that it is the only cause of this disease. Obviously there is the factor of internal predisposition which must exist, since not everyone who smokes develops lung cancer. Obviously, too, there are other exogenous factors that may produce cancer of the lung. Among these are a number of occupational exposures. There is also evidence that general air pollution and/or motor exhaust fumes may be a contributing factor..."

and Macdonald (2084):

"There is a growing body of evidence in the past decade or more to indicate that multiple factors are operative in setting the stage for a considerable variety of cancer in man. There is a rather small group of human cancers in which only a single environmental agent is apparent as a predisposing cause of any significance; more commonly there are two or more separate factors frequently of entirely different nature which combine to increase the likelihood of cancer developing in the individual. This is the principle referred to as cocarcinogenesis, indicating the inability of a single agent to produce cancer, but when combined with another or other agents a cumulative effect is created which may lead to development of cancer. Some of these factors are extremely weak carcinogens, or predisposing agents to cancer."

e. Is the Claimed Increase in Lung Cancer Incidence Real or Illusory?

Obviously, if there has not in fact been an increase in the incidence of lung cancer accompanying the great rise in cigarette consumption (beginning after 1920), the cigarette theory is seriously compromised. Cornfield et al. (3409) freely concede this.

The rising recorded death rate from cancer of the lung in all countries that have sufficiently detailed mortality statistics has been dramatic (615-A, 1104-A, 3409). This fact has been noted by a host of writers, including Ochsner, Wynder, Graham, Shimkin, Hammond and Lillienfeld. That this increase is a fact and not a spurious result of statistical classification now appears to be accepted by the numerical weight of authority. On the other hand, a contrary view is held by some eminent men, such as Rigdon (1911-A), Macdonald (2084) and Little (2082). There are also men who, while agreeing with the view that there has been a real increase, express reservations regarding its extent and timing; for example, Hueper (970-B), and Gilliam (944-A) are of this school.

The evidence refuting the claim that there has been a real increase in lung cancer mortality

falls into the following categories:

1. Improved methods of diagnosis.
2. The general unreliability of certifications of causes of death contained on death certificates.
3. An aging population.
4. A population increasing in size.

Rigdon (1413) has shown, as mentioned before, that there is a significant correlation between the population to physician ratio and the population to hospital bed ratio and the number of reported deaths from lung cancer in the United States. He also asserts that the combination of better diagnoses, decrease in the number of deaths from infectious diseases by both prevention and therapy, and the increased aging of the population seem to be more significant factors than any one or group of carcinogens to account for the apparent increase in the frequency of carcinoma of the lung.

In a recent review of the lung cancer literature during the period 1900-1930, he and Kirchoff (3016) observed that primary lung cancer was first recognized about 1810, and that its occurrence has increased steadily since that time, as manifested by the recorded relative frequency with which it was

recognized in the clinic and at post-mortem. Cornfield, et al. (3409) acknowledge that this statement is undoubtedly correct, but claim it does not constitute evidence against a true increase in the incidence of the disease during the whole, or a more recent part, of the past century.

Rigdon on another occasion correlated the increased incidence with new techniques for diagnosis. He adverted to the invention of the X-ray in 1895, followed by the bronchoscope and, in 1933, the first successful operation for lung cancer. The latter, he observes, immediately focused attention on the problem of lung cancer.

The effect of improved diagnosis is vividly demonstrated by Rosenblatt (1927-A) in the following language:

"History has repeatedly demonstrated that whenever an inaccessible cancer becomes accessible, the incidence automatically increases. Prior to 1930, the clinical facilities for the diagnosis of lung cancer were few and far between even in thoracic disease hospitals. The perfection of diagnostic tools (exfoliative cytology, bronchoscopy, radiology and exploratory thoracotomy) occurred within the past 25 years. This is obvious to all who have worked through this era. Many hospitals now perform more bronchoscopies per day than they did per year a quarter of a century ago. The records of a world-famous cancer institute show that its staff recognized only about half a dozen lung cancers annually before 1930."

IV-B-98

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Rosenblatt has also said:

"No matter how remote the community, the establishment of a diagnostic center inevitably results in a greater incidence of lung cancer. A survey in East Pakistan disclosed 20 new cases over an 18-month period; only 2 of the new cases were heavy smokers, and these used the hukka, a water-filtered pipe."  
(1927-A)

Gilliam (944-A) studied the potential effect of improved diagnosis on the course of the death rate from lung cancer. He found that even assuming two percent of the deaths certified in past years as tuberculosis or other respiratory diseases were really due to cancer of the lung,

"...all of the increase in mortality attributed to cancer of the lung since 1914 in U. S. white males and females cannot be accounted for by erroneous death certification to other respiratory diseases without unreasonable assumptions of age and sex difference in diagnostic error."

Gilliam's computations reduced the respective 26-fold and seven-fold increase in lung cancer mortality among males and females, between 1914 and 1950, to the more modestly estimated dimensions of four-fold and 30 percent, respectively, which Cornfield *et al.* (3409) treat as the lower bound on the magnitude of the true rate of increase.

The effect of aging on the incidence of lung cancer has also been considered by Rosenblatt (1927-A), among others. He has stated that since there are more

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older people among us today, there are more potential candidates for cancer of the lung in view of the recognized affinity of the disease for older people.

Dunn (780) comments that diagnostic improvement and population aging could conceivably account for even a very large general increase in the reported mortality rate, but that the following factors are inconsistent with this explanation:

1. The size of the increase is very different for men and women; disproportionate increases have since the early 30's greatly widened the gap between the rates for the two sexes.
2. The rates of increase vary considerably for different age groups.
3. The rates are continuing to increase sharply from year to year without a commensurate improvement in methods of diagnosis.

Dunn concluded that only one-sixth of the over-all increase in lung cancer mortality among males in the U. S. (from 4 to 24 deaths per 100,000 males between 1930 and 1951) could be attributed to an aging population.

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Similar findings were noted by Doll (918-B) for England and Wales, where observations on lung cancer mortality date back to 1900; the 1953 mortality rate for both sexes, 34 per 100,000 population, was 43 times the corresponding 1900 rate, 0.8 per 100,000 population. Thus, he reasons, allowance for the increased average age of the population could account for only half this rise in lung cancer mortality, with a 24-fold difference between 1900-1953.

As Cornfield et al. (3409) point out, however, an aging population does not affect the age-specific death rates and cannot account for the phenomenon of increasingly higher lung cancer mortality at all ages throughout the life span, which has occurred among successively younger groups of males born in the U. S. and England and Wales since 1850. A similar but less pronounced cohort displacement has been shown for females. In short, they claim this increasing rate among younger cohorts, the rising ratio of male to female deaths, and the magnitude of the current increasing mortality rate (see Doll (918-B)) make it difficult to contend that the increase is attributable to improved diagnosis alone.

IV-B-101

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Hueper (970-B) accepts the view that there has been a true increase in the incidence of lung cancer, but regards the increase as dating back to 1900 - well before the widespread use of cigarettes. This he considers to be evidence contradicting the cigarette-lung cancer relationship. The retort of Cornfield et al. (3409) is that Hueper's contention would have "crucial import" only if cigarette smoking were alleged to be the sole cause of lung cancer. But we believe that Hueper's claim of a "real, definite, and progressive increase" in the frequency of lung cancer starting in most industrialized countries around the turn of the century is strongly suggestive of the existence of another factor, which may have grown common about the same time as cigarette smoking and by an accident of timing have inadvertently focused blame on smoking. In other words, Hueper's thesis could be consistent with tobacco being a contributory cause, as claimed by Cornfield, et al., and it is equally consistent with complete innocence of tobacco. And his case for an increase beginning as early as 1900 is substantiated by the reports of autopsies by numerous leading pathologists in Europe, where autopsies have for many years been the rule rather than the exception (970-B).

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If one accepts the contention of Rigdon (1911-A) and Macdonald (2084) that the apparent increase in lung cancer incidence is primarily due to better diagnosis, better medical facilities, etc., then the cigarette smoke-lung cancer association would appear to be fortuitous.

On the other hand, if one accepts the contention of Hueper (970-B) that the increased incidence of lung cancer is real but began around the turn of the century, then some agent other than cigarettes must be at fault - either in combination with tobacco or separately. The rapid rise in lung cancer incidence that occurred in the 1920's and 1930's could be explained by the increased consumption and/or production of many products besides cigarettes, e.g., automobile tires, fuel oil, miles of asphalted roads, automobiles, etc. Hammond (650-D, 2244) discounted these commodities as being responsible for the increased incidence of lung cancer. Hueper has carefully documented a number of these as being coincident with the increase in lung cancer (970-B).

If Hueper is correct, there must be some explanation for the decreased lung cancer incidence in people over 60 other than the glib assertion

(advanced by some of the anti-tobacco group) that such people were not exposed to cigarette smoking when they were young. Parenthetically, one might properly ask why these people do not suffer from lung cancer anyway, in view of the fact that they were only about 30 in 1920 when cigarette smoking began to acquire large numbers of adherents. Nor does this explanation for the absence of lung cancer among older persons jibe with the statistical findings linking smoking with other types of cancer, in view of the fact that one's chances of contracting these increase with age.

Rigdon (1911, 1911-A) also claims that basing the frequency of cancer of the lung on records obtained from death certificates may contribute to the illusion of an increase, because such records are not always accurate. According to him, the medical profession will generally admit that the diagnosis of cancer of the lung is difficult because death occurs in many cases prior to the examination necessary to determine whether the cancer originated in the lung or whether it started elsewhere and metastasized to the lung. In fact, the site of origin is sometimes difficult to establish even by autopsy. Noting that the significance of conclusions derived from statistical studies cannot be any better than the accuracy of the original

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data, Rigdon has unequivocally stated that the studies on which the relation of cigarette smoking to lung cancer was based did not justify the conclusions drawn by their authors.

Ackerman (1-A), an associate of the late Dr. Graham at Washington University School of Medicine in St. Louis, wrote in a standard textbook on cancer published in 1954 that death statistics are not very accurate because death certificates are usually based on clinical assumption and seldom on confirmed pathologic findings. He cited in support of this view a study made by Willis (770) in 1948 of 1000 autopsies of cases diagnosed clinically as cancer, in which Willis found that 57 cases had no cancer, and 31 percent of the balance had been correctly diagnosed as cancer but misdiagnosed as to site of origin. Willis also found that errors of diagnosis were considerably greater for inaccessible areas of the human anatomy.

Ackerman is of the opinion that the increase in reported deaths from all cancers is more apparent than real because of improved diagnosis, increased cancer-consciousness on the part of the public and medical profession, and the aging population. He notes, however, that there appears to

be a true increased incidence of certain forms of cancer, such as cancer of the lung and large bowel.

Greene (1664) has recorded his doubts as to the reality of the increased incidence of lung cancer as follows:

"Many believe the frequency of lung cancer has increased during the past two decades and, on that basis, a search has been made for some environmental factors showing a parallel increase. It should be emphasized, however, that there is some question as to whether the purported increase is real or only apparent, that is, has the incidence actually increased or are we only now becoming aware of the true frequency of the disease? This is a difficult question, and there is much doubt in critical minds as to whether or not a true answer is possible."

He believes that statistics based on death certificates are practically valueless, and that the only material suitable for analysis is that derived from biopsy or from autopsy reports. But figures so obtained, he points out, are necessarily based on a hospital rather than a general population and are accordingly biased as they represent the incidence among people sick enough to be brought to a hospital. The number of such people varies with many extraneous, unrelated factors, including hospital facilities (see Rigdon above) which have been greatly augmented during the past 40 years. Nevertheless, he

IV-B-106

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acknowledges that the figures derived from such a population do indicate an increased incidence, but here again he professes not to know whether or not the increase is due to the coincident improvement in diagnostic facilities.

The fact that the major portion of our population is in the 40 and over age, as compared to the predominantly youthful population of a generation ago, means that more men now reach the age when cancer and coronary diseases strike. He concludes that the factor of a rapidly aging population no doubt accounts for a considerable part of the increased incidence of lung cancer.

Lew (672, 995-A), statistician for the Metropolitan Life Insurance Co., commented on the increased incidence of lung cancer as follows:

"During the past 25 years, the white male mortality from respiratory cancer, adjusted for age distribution, increased five times. An increase of this magnitude and rapidity appears greater than can be accounted for solely by better diagnosis, case finding, and reporting, especially as no other site of cancer has shown as large a proportionate increase. If all the increase in respiratory cancer were due to better detection, and reporting, it would mean that physicians practicing 25 years ago were able to identify at most only one out of five cases existing at that time. Furthermore, the increase is continuing despite the fact that the disease is now more generally recognized \* \* \* ."

IV-B-107

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With respect to the male-female incidence, Lew noted:

"\* \* \* it is difficult to see why physicians should be able to diagnose respiratory cancer more readily in one sex than the other."

and he concluded his remarks as follows:

"The geographic variations in respiratory cancer mortality in the general population \* \* \* indicate that some environmental factors may be contributing to produce the higher death rates found in the most urbanized and industrial states \* \* \* . There is reasonably convincing statistical evidence that a number of different factors may be implicated in the rise in the incidence of respiratory cancer."

IV-B-108

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## 7. Summary of Criticisms

The following questions point up the various criticisms of the statistical studies, both retrospective and prospective:

1. Has the incidence of cancer of the lung really increased?
2. Is the incidence of cancer of the lung due to a single factor or to multiple factors?
3. Is the incidence of cancer of the lung related to geographical location?
4. Is an apparent association between cigarette smoking and lung cancer equivalent to a cause-and-effect relationship?
5. Does an anomaly exist between the male to female ratio of incidence?
6. Are socioeconomic considerations important in the incidence of lung cancer?
7. Are the statistical studies, both retrospective and prospective, valid in respect of questionnaire, methodology, controls, etc.?
8. Is the parallelism between increased consumption of cigarettes and the increased incidence of lung cancer meaningful?
9. Are the lung cancer-cigarette smoking statistical studies compatible with urban-rural

variations in incidence of lung cancer?

10. Is the constitutional make-up of a person who develops cancer of the lung the same as the constitutional make-up of a person who smokes excessively?

11. Are the results of the statistical studies compatible with laboratory evidence?

12. Is the spectrum of diseases noted by Hammond and Horn (2534-A, 2534-B) which apparently are associated with excessive cigarette smoking an indication of the invalidity of the statistical method and/or study?

13. Is there a reasonable explanation for the differences in tobacco consumption versus lung cancer incidence in various countries throughout the world?

IV-B-110

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C. BIOLOGICAL STUDIES ON TOBACCO PRODUCTS

1. ROLE OF ANIMAL EXPERIMENTATION IN CANCER RESEARCH

The use of animal experiments in cancer research is extensive. One article attempting to collect references with regard to experiments with carcinogens lists a total of 1740 papers (1280). In addition, the Public Health Service has published three large volumes entitled "Survey of Compounds which Have Been Tested for Carcinogenic Activity". A selective review of this literature by a layman leaves the impression of a confused and inconclusive state of knowledge. Not only are the results of various experiments inconsistent, but their value in relation to human beings (i.e., extrapolation) is in itself a subject of controversy. This section of the memorandum will attempt an objective review of the various theories with regard to the role of experimental research in cancer and the results of such research.

The introduction to the second edition of the Public Health Service publication "Survey of Compounds which Have Been Tested for Carcinogenic Activity 1951" discusses the use of animal experiments which test substances for carcinogenic activity (see also Rigdon (1911-A)).

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"This is a convenient place to discuss one of the pitfalls in the use of a survey like this to affirm or deny a proposed theory of carcinogenesis or a fancied correlation between carcinogenicity and chemical structure. There is a tendency on the part of some to consider carcinogenicity or lack of carcinogenicity as characteristic properties of chemical compounds. It is, sometimes, not realized that lack of carcinogenic potency implies such a lack only under limited experimental conditions. This has been well emphasized by Shear and Leiter (J. Nat. Cancer Inst. 2, 254 (1941)) as follows: '\* \* \* it is desirable to bear in mind that the statement to the effect that given compounds are noncarcinogenic does not necessarily mean that they are incapable of inducing malignant tumors; it means only that the compounds did not give rise to tumors under the conditions of certain experiments of restricted scope. For example, the hundreds of such compounds examined for potency in Kennaway's laboratory in London and in this laboratory have, with few exceptions, been tested in mice only. The small number which were tested in several species of animals have given results which make clear that there are pronounced differences in the response of different species to the action of compounds carcinogenic in the case of the mouse. Moreover, there is evidence that some compounds which were negative in the mouse can induce tumors in other species \* \* \*

'Furthermore, in the mouse itself, it is now abundantly evident that different tissues respond differently to the same compound. Some compounds have given negative results when applied to the skin but have been quite active when injected subcutaneously. With other compounds both techniques have given positive results but have brought out pronounced differences in the response of the skin and of the subcutaneous tissue. Compounds that are potent for the skin and subcutaneous tissue were found to be inactive when introduced directly into the liver \* \* \*. The susceptibility of the lungs \* \* \* does not necessarily parallel that of the skin or the subcutaneous tissue.

'The mode of administration may also influence the results markedly. The dose may be too high as well as too low, and the most effective dose for one compound is not necessarily the same as that for another closely related one. The solvent or vehicle may affect the results profoundly. Media of complex nature, such as lard or sesame oil, may contain anticarcinogens or co-carcinogens\* \* \*, and even chemically homogenous vehicles may give different results\* \* \* with the same dose of the same carcinogen administered to the same tissue of the mouse.

'Moreover, the sex of the animal is not without influence on the results\* \* \*. It is also conceivable that the life span of the mouse is a factor. Since some compounds which were negative during the first year gave rise to tumors during the second year of the experiment, it is possible that some compounds which gave negative results in the mouse might give positive results if its life span were longer. Diet, too, may be an important factor\* \* \*.

'For these various reasons the considerations, stated in an earlier paper\* \* \* in a discussion of the concept "average time" of the latent period of carcinogens, are also applicable here, viz, the term "carcinogenic potency" as used in these studies is not to be considered as an invariable property inherent in a compound but is merely a summary of the results of particular experiments and is valid only for animals of the species, strain, sex, age, diet, etc., of the particular animal employed, as well as for the dose, menstruum, mode and site of application, etc., of the compound in question\* \* \*. Conclusions regarding the potency of any given compounds should therefore be interpreted in the light of the data upon which they are based.'

Another pitfall is the attempt to carry over, without reservation, to man, conclusions based on animal experiments. We do not know whether man is more or less susceptible than mice to particular carcinogens. Some animal species, such as the rat, rabbit and dog, are much more resistant to certain chemical carcinogens than is the mouse, and vice versa, while in the monkey none of the powerful

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carcinogens has been shown to produce tumors. It would, therefore, be dangerous to conclude that man is resistant or susceptible to a given carcinogen merely on the basis of experiments with a single species of laboratory animal since we also know of several chemical agents which, as occupational hazards, are responsible for some human cancer and which have so far yielded negative results in laboratory animals. In the light of species specificity, a given compound, whether or not it is carcinogenic to animals, may or may not be capable of producing cancer in man. In view of the large number and variety of carcinogenic compounds, we must regard this multiplicity of newly developed and yet to be developed drugs, dyes, food additives and other chemical compounds with which we come in personal contact as possible cancer hazards, and we must reserve judgement on specific compounds until they are adequately investigated." (pp. 1-2)

See also (2664-A).

Similar views are stated by Shubik in an excellent review (1283). However Shubik does feel that:

"There is no way yet of deciding the correct species to be used for a particular carcinogenicity test, since results in the mouse, rat, or any laboratory animal may possibly have no bearing on the human hazard. This, of course, in a consideration invoked in any animal test of biological activity, and the criticism does not apply any more to carcinogenicity than to any other form of toxicity. Experimental tests with carcinogens that do parallel experience with human carcinogenesis, even to the point of yielding tumors of the same morphological type at the same site, are by no means infrequent, as with coal tar, aromatic amines, x-rays. It must be emphasized, however, that these parallels are very broad in outline and cannot give us precise information of the quantitative type often desired. Species variations are common in the qualitative nature of the results and even in the presence or absence of an absolute response. It must be recognized that no definite negative

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results for the human can be inferred from tests restricted to a single species. Isolated positive tests can be used as indicators of possible hazards but are rarely adequate as the basis of hard and fast rulings. There is no reason for recommending the use of particular species except in instances of compounds allied to known carcinogens. \* \* \* (pp. 729-730)

However, Shubik did emphasize the value of animal experiments.

"Experimental findings of carcinogenicity do not prove that the agent in question has a similar role in man; such findings do, however, provide a cogent warning of a possible similar action. The number of parallels between human and animal carcinogenesis are now sufficient for appropriate use to be made of such indications. There are few who would recommend acetylaminofluorene for uncontrolled usage, and yet no human data on the activity of this substance are, fortunately, available." (p. 737)

Other investigators, however, are willing to ascribe greater importance to animal experiments. In a review of the smoking-lung cancer problem Cornfield et al. (3409) admit that direct extrapolation from one species to another is unjustified. However, since the results of animal experiments are fully consistent with the human clinical, statistical and epidemiological data, they are said to attain greater status.

The two investigators who give most weight to animal experiments are Wynder and Kotin. Their interpretation of the human and experimental data is similar; the only difference is that Kotin feels air

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pollution a most important factor; Wynder, cigarette smoking. They both accept the multiple etiology of respiratory cancer and agree that both factors play a role in carcinogenesis. Kotin's view with regard to the role of animal experiments was expressed in a speech before the National Conference on Air Pollution in Washington, November 19, 1958 (3828).

"Certain epidemiological facets of the increasing incidence of lung cancer suggest that the atmospheric environment may be causally associated with this observed increase. Epidemiological data serve to indicate the areas for experimental biological efforts. The physical sciences provide the facilities for duplicating the naturally occurring environment in the laboratory. With knowledge gained as a result, laboratory biological investigations can be properly formulated and implemented. While these are necessarily primarily limited to animal species, much significant information can be obtained. Animal studies can and do provide numerous advantages. The first and most obvious, of course, is obviating the necessity of prolonged human experimentation with toxic agents. Second, the use of large numbers of animals permits the study of sequential changes in the development of an adverse response. Careful assessment of host resistance factors in overcoming these negative effects is also frequently possible. Third, protective or therapeutic measures aimed at controlling the effect of air pollutants can be quantitatively studied. Fourth, within limits, practically any state of human health from the young and vigorous to the old and partially decompensated can be reproduced in animals." (pp. 232-3)

Wynder wrote in 1959 (3525).

"The importance of laboratory work is not to prove that smoking is a cause of cancer in man. Such proof can only come from human epidemiological

investigation. Laboratory research can, however, contribute to, and give a logical explanation for, the human findings. Just as an animal experiment cannot disprove that a given factor causes cancer in man because of possible species differences, so, by itself, an experiment cannot prove a given agent to be carcinogenic to man. It is primarily as a corollary to the human findings that the animal experiment has its significance. The basic tasks of laboratory research, which are of a biological and chemical nature, are to identify the specific agents in a given product that produces cancer and to devise ways and means whereby such agents can be reduced or removed. In so doing, we can only assume that the agents responsible for the activity in animals are also responsible for the human activity. In view of the many similarities established for tumour growth in animals and man, such an assumption, though it cannot be proved, stands on a firm foundation."

IV-C-7

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## 2. SKIN PAINTING EXPERIMENTS USING TOBACCO PRODUCTS

In order to present the material in more manageable form, a more or less arbitrary organization will be followed. Experiments with regard to direct application of tobacco products to the skin or by subcutaneous injection will be discussed. Experiments involving other substances will be discussed under Environmental Factors. Experiments with regard to the lung and other internal sites will then be discussed.

IV-C-8

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a. Positive Results

The first experiments with tobacco as a possible carcinogen date back to the early 1900's. However, it was not until 1953 that the first significant results were obtained. Wynder, Graham & Croninger (475) reported in December of 1953 that CAF-1 mice painted with tobacco smoke condensate showed a strikingly higher incidence of skin cancer than untreated mice. The authors reviewed prior attempts to induce cancer with tobacco tar which were in the most part unanimously negative.

One of the earliest investigators of the carcinogenic activity of tobacco tars, distillates, etc. was Brosch (52), who observed in 1900 proliferation in guinea pigs painted with "tobacco juice". In 1911, Wacker and Schminke (453,453-A) injected tobacco tar obtained from pipes into rabbits and observed similar proliferation. Schreus et al. (389) in 1912 observed such changes in mice skin painted with denicotinized tobacco tar.

In 1923, Hofmann et al. (180) observed only

hair loss in mice painted for two weeks with denicotinized tobacco tar.

In 1928, Helwig (159) employed tobacco tar from pipes in rabbits by injection and on mice by skin painting. Extensive proliferation was observed in the rabbits; ulceration in the mice. In another experiment using a tobacco distillate, mice developed benign ulcers after 8 months' treatment.

From 1930 on, Roffo published many papers on the carcinogenic activity of tobacco tars obtained by distillation processes (345, 346, 346-A, 349, 350, 351, 357, 362, 365). In 1941, he also postulated on the basis of spectrophotometric evidence that 3,4-benz-pyrene was a constituent of his distillate (368). However, Flory in 1941 (127) was unable to duplicate Roffo's experiment. He obtained some papillomas (benign epithelial tumors) and carcinomatoids (a growth resembling cancer) in his rabbits but no true cancers. He suggested that Roffo's changes were really similar to the ones he obtained and not true cancers.

IV-C-10

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In 1931, Chickamatsu (65) obtained a "cancroid" on the ear of a rabbit painted for 225 days with tobacco tar. A year later, Bogen and Loomis (47) reported negative results as did Cooper et al. (78).

Lu-Hu-Fua (270, 271), in 1934, using destructive distillates from tobacco reported three carcinoma in rabbits' ears. Animals treated similarly with coal tar developed four carcinoma at site of application.

In 1935, Schurch et al. (392) failed to produce tumors in mice or rabbits painted with nicotine-free tobacco tar. Two years later, these authors (393) reported one carcinoma in one rabbit treated for four years with cigar tobacco tar. In 1937, Taki (425), in an experiment involving 104 mice treated with tobacco tar, reported two epitheliomas, 3 papillomas.

In 1940, Sugiura (421) described negative results obtained in painting and injection experiments involving mice, rats and rabbits.

In 1946, Jaffe et al. (208) claimed that they had produced sarcomas in animals by the intraperitoneal

injection of tobacco tar solutions. Subcutaneous injection of this material did not give subcutaneous tumors.

Impressed by the clinical and epidemiological evidence linking smoking with lung cancer, Wynder and his associates sought to produce squamous cell carcinomas on the skins of CAF-1 mice with tobacco smoke condensates. They built a smoking machine and an apparatus with which to condense the tar from the smoke. Combustion temperatures were carefully noted. The backs of the mice were shaved and painted three times a week throughout their lives with tar in an acetone solution. Of 81 tarred mice 59% developed papillomas and 44.4% developed epidermoid cancer of the skin. While stating that "animal data do not necessarily confirm or deny human data", the authors felt the experiment confirmed the human data on lung cancer (475).

Using that experiment as a springboard, Wynder et al. (800-B) conducted a series of experiments designed to further understanding of the carcinogenic effect of tobacco tar. They first tested different strains of mice,

IV-C-12

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C 57 and Swiss. Cancers were produced in both strains but the results were not nearly so striking as those obtained with the CAF 1 strain.

The next experiment of Wynder et al. indicated that where painting was stopped before changes occurred in the skin, CAF 1 mice nevertheless developed papillomas and cancers after a considerable latent period. Wynder claimed that this experiment confirmed the statistical data that ex-smokers get more cancer than non-smokers (2074).

These investigators then sought to induce cancer in rabbits with their tobacco smoke condensate (1354, 2231). New Zealand albino rabbits, 65 in number, were painted five times a week on the inner ear surface. The first papilloma (a benign epithelial tumor) appeared in nine weeks and by the eighth month 50% had papillomas, all at the end of 23 months. The first cancer appeared in the 21st month. Five cancers developed altogether. Wynder feels that prior experiments with rabbits were negative because the doses were too small and the paintings did not continue for a long enough period.

Wynder and his associates next turned their attention to other tobacco products. They obtained tar condensate from cigars, pipes and all-tobacco cigarettes

(cigarettes wrapped in tobacco leaf rather than paper). they concluded that the cigar and pipe tars were slightly more carcinogenic than cigarette tars. This was inconsistent with the human data regarding lung cancer, but consistent with that for mouth cancer. Wynder explained away this inconsistency on the basis that cigarette smokers inhaled, while cigar and pipe smokers did not (3253).

Subsequently, in 1959, Croninger and Suntzeff (3577-A) reported the transplantation of tobacco tar-induced skin cancers in other mice. Transplants were almost all successful in the same strain, but negative in different strains of mice. The authors concluded that the results were conclusive evidence that their tar-induced tumors were true cancers.

Concurrently with these experiments Wynder was attempting to determine what substance or substances in the tobacco tar was responsible for the carcinogenic activity on the mice. He and Wright (2054-E) subjected the cigarette tar to several types of tests: chemical fractionation, molecular distillation and ion exchange separation. The various fractions of tar were painted on mice and rabbits. Because of the great toxicity, nicotine was removed from the tars so that the animals could survive. The various fractions are normally referred

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to as the basic, neutral and acidic. All of these fractions produced some carcinogenic activity; the acidic and basic showed the lowest activity, while the neutral proved the most carcinogenic. Wynder discovered 3,4-benzpyrene in the various fractions but in insufficient amounts to explain the results. The article states that there are probably unestablished carcinogens which are responsible. Further experiments (2448) with benzopyrene proved that there was not enough in tobacco tar to cause the animal results.

Wynder et al. (1450,2447) then sought to establish a minimum dose of tobacco tar necessary to cause carcinogenic changes in laboratory animals. The experiment was suggested by statistical studies which showed that light smokers suffered from less lung cancer than heavy smokers. The strength of the tar solution and the number of paintings was varied for Swiss mice. A decrease in the frequency of painting showed a significant decline in tumors and an increase in the latent period. Mice painted for 9 months only developed cancers long after the painting stopped. Wynder concluded that cancer and dosage are in direct proportion and that a four-fold decrease in smoking would all but eliminate cancer production.. He also felt this experiment explained past failures to produce cancer with

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115

tobacco tar since the cancer investigators used less than the "threshold dose". Elsewhere, Wynder (3525) has stated:

"\* \* \*when testing a substance suspected to be only weakly carcinogenic, the substance should be applied in maximum concentration and over a maximum period of time."

Wynder concludes that these results are consistent with the statistical data that show a greater risk with higher consumption of tobacco for humans.

Wynder (2447-A) also turned his attention to filter cigarettes. He tested filtered and unfiltered cigarettes for a difference in carcinogenic activity on mice. The results showed that on a gram to gram basis the carcinogenic activity of the filter cigarettes was similar to that of the unfiltered. There were no statistically significant differences in papilloma and cancer production between the mice painted with unfiltered cigarette tar and filtered cigarette tar. Wynder concluded that the filters then in use did not remove the carcinogenic agents which affect mice.

In 1959 study by Haag, Larson and Finnegan (3647) indicates that plain cellulose-acetate soft paper mechanical filters were much less efficient than a charcoal treated filter in removing irritating properties of smoke as measured by its edema-producing potency on the

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conjunctiva of anesthetized rabbits. However the charcoal filter was only very slightly more effective than the plain filter in removing the particulate phase components, notably nicotine and tar.

Wynder then studied different tobacco types to determine whether there was any difference in the property of their tars. (2446-A) Burley, Virginia, Maryland and Turkish tobaccos were tested. Burley had the most tar and nicotine, Turkish the lowest. There was no significant difference in the production of papillomas and cancers among the mice exposed to the different tobacco tars. The authors concluded that the effect of these four types of tobaccos on CAF 1 and Swiss mice did not significantly differ. This was consistent with the early work of Roffo (362) which showed little variation between Turkish tobacco and Kentucky burley.

During the previous studies there were indications that the burning temperature of the tobacco had an important effect of carcinogenic activity of the tar. Wynder et al. (2722-A, 3372-A) sought to test this factor by burning cigarettes at various temperatures. Cigarettes were extracted with hot hexane and further extracted with hydrochloric acid. The resulting substance was then pyrolyzed at temperatures from 560° C to 880° C. The experiment confirmed the established concept that

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carcinogenic polycyclic hydrocarbons can be formed by pyrolyzing organic matter. No carcinogenic activity was noted from tar burned under 640° C. The production of carcinogens increased with the temperature until the maximum was reached at about 800° C. At higher temperatures the carcinogenic property of the tar declined. It was determined that burying the cigarettes closer to the end did not result in a geometric increase in the production of tar but, naturally, the more the cigarette was smoked the greater the production of tar.

Because the mouse painting experiments required much time before papillomas and carcinomas developed, Wynder et al. (1990) sought to devise a short-term test for carcinogenicity. Initial activity in the prior experiments was noted in the sebaceous glands which are immediately beneath the skin. Changes in those glands are closely associated with epidermal carcinogenesis. The backs of mice were painted for 5 to 10 days, depending on the concentration of the solution. The animals were then sacrificed and section of the skin inspected. The stronger solutions had destroyed most of the glands while the less strong solutions showed increasingly less destruction. The result was compared by those obtained by Wynder and Wright (2054-E) and there was 84% agreement. The authors conclude that within limits the tests can

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register activity or nonactivity but cannot replace long-term painting.

Mellors et al. (1825-A) arrived at similar results with tars obtained from Wynder. Mice were painted with varying doses and frequency and sacrificed at different intervals. The skin was examined by fluorescent microscopy. The more active the tar fraction used, the more effects were observed. The most carcinogenic fractions promptly localized in the sebaceous glands.

Subsequent chemical analyses have indicated other polycyclic hydrocarbons suspected of being carcinogenic (cf. Wynder (3525); see separate section herein on Chemical Studies of Tobacco Smoke). However, even these substances cannot explain the results of the animal experiments. Thus Wynder still believes that there is an unknown carcinogen in tobacco tar, although he states the possibility that the summation of the carcinogens presently known may be sufficient. Greenstein (142), discussed more fully in the section Chemical Studies of Tobacco Smoke, indicates that application of a strong and a weak carcinogen of similar configuration reduces the effect of the former. And see Riegel, Cancer Research, 11, 301 (1951), Steiner, id. 15, 632 (1955).

Several other investigators (1289, 2199, 2530, 3179, 3388, 3644) have been able to obtain papillomas

and carcinomas on mice with cigarette tar. However, no one (including Wynder himself) has been able to achieve the number or percentage of cancer achieved by Wynder in his first experiment (475).

Orris et al. (3179) compared the tar condensate prepared at New York University with that prepared by Wynder at Sloan-Kettering. The Sloan-Kettering tar contained three to four times as much polynuclear aromatic hydrocarbons and produced 10% more cancers. The authors concluded that both tars were definitely but not strongly carcinogenic and that known carcinogens cannot explain their activities.

Koprowska et al. (3680, 3680-A) painted cigarette tars on other sites in mice. When applied to the uterus, changes were produced which appear to be similar to the early stages of cancer. However, more testing is necessary to determine whether these changes will actually become malignant. Neoplastic lesions were also produced in the cervical and vaginal mucose of C3H mice when tar was applied intra-vaginally five times weekly for 44 weeks (3290).

One other experiment has been conducted which, to some extent, is inconsistent with Wynder's theory of carcinogenesis. Cramer and Stowell (CANCER RESEARCH; 3, 36-42 (1943)) produced local cancer on the skin of Swiss

mice with one large dose of 20-methylcholanthrene. The authors state that this experiment compromises the theory that prolonged exposure is necessary to result in cancer. This could have significance with regard to occupational hazards in man. If a human is subjected to a large occupational hazard early in life, it might be a significant factor in cancer production although the exposure was of limited duration.

IV-C-21

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b. Negative results with tobacco

(1) Mouse painting and ingestion

Several experiments to produce cancers on mouse skin with tobacco tar have been completely negative. In 1954 Passey et al. (1046-AA) recorded negative results. Passey suggested that the different result from Wynder might be due to the fact that Wynder's cigarettes were smoked at a much higher temperature. He noted, however, that his temperature were closer to those in human smoking, about  $720^{\circ}$  C. (It should be noted that Touey et al. (1293) report a temperature of  $874^{\circ}$  C. for cigarettes. The lower values obtained by other smokers are explicable by the size of thermocouple used).

Hamer and Woodhouse (955-A) also reported negative results in 1956. In this experiment the mice were not clipped or shaved and the solutions were applied with a dropper rather than a brush. The experiment lasted 18 months but no carcinogenic effect was noted. A different mouse strain than Wynder's was used, but the strain is susceptible to ordinary known carcinogens. In addition, British cigarettes were used rather than American and the investigators obtained only half the

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tar Wynder got from the same number of cigarettes.

In 1957 Passey (2864) again reported on his continuing studies in which he compared the tar obtained from English and American cigarettes. This time Passey used the same mice as Wynder. Although he obtained one carcoma (a malignant non-epithelial tumor), the results were difficult to interpret because the strain was subject to a marked degree of spontaneous ulceration. Passey concluded that this strain was not suitable to tests due to that condition. Also, leukemia frequently was in evidence and pulmonary adenomata (a neoplasm, or new growth, of glandular epithelium) occurred in nearly every animal over a year old.

When Lyons et al. (2844-A) injected neutral aromatic fractions of smoke tar into the thigh muscles of strain C mice, no tumors developed. Injections with 20-methylcholanthrene (not yet found in tobacco tars) have yielded tumors which indicate that the technique is satisfactory for the bioassay of potential carcinogens. This experiment has been continued and negative results were also reported in 1959 (4167).

IV-C-23

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Holsti and Ermala (968-A) have painted the lips and oral mucosa of mice with tobacco tar for 12 months. Although no activity was noted on the lips or oral cavities, the painted mice showed a marked increase in bladder papillomas and cancers. The authors suspect that a carcinogenic agent in the tobacco tar is absorbed through the gastrointestinal tract and excreted in the urine, causing the changes in the bladder. They also note that the period of treatment here was relatively short.

The reasons for the difference between the results of Wynder and the British investigators have been noted above. Because Wynder shaved his animals and some of the British investigators did not, it has been suggested that trauma to the skin caused by repeated shaving explains the difference. As with all other points in this perplexing field, experiments show that trauma has an effect in cancer production and the contrary. Rigdon (1411) applied 20-methylcholanthrene to ducks after plucking feathers from the skin and also to unplucked ducks. The plucking increased the activity of the carcinogen.

However, Bock and Moore (3388) shaved and painted mice with tobacco tar and shaved, painted and rubbed the skin of others with sandpaper. Those mice



whose skin was irritated by sandpaper showed no significant difference in papilloma and cancer production. However, those mice which were subjected to intense radiation developed many more papillomas and cancer. These authors concluded that their tests support the view that tobacco tar is a weak carcinogen for mouse skin, and that the results cannot be extrapolated to man.

Gellhorn (2780) sought to test whether tobacco tar was a cocarcinogen with air pollution and perhaps other factors. Using tobacco tar condensate, benzpyrene and croton oil, he painted these substances on the backs of Swiss and Paris R III mice alone and in different combinations. He found that the tar had little effect by itself which agreed with the British experiments discussed previously. However, when tobacco tar was mixed with 3,4-benzpyrene or croton oil the mixture had much greater effect than either of those substances alone. The greatest effect was achieved with 3,4-benzpyrene and tar. Thus Gellhorn suggests that tar has a cocarcinogenic effect.

Some experiments have shown that tobacco tar has an inhibiting effect on the production of cancer in some sites. Investigators have determined that exposure to smoke or tar inhibits the well-established carcinogenic sequence in liver cancer in rats when induced by known carcinogens (3136).

(ii) Embryonic tissue transplants

Greene (1664, 2075-A) has transplanted embryonic mouse and human lung tissue infiltrated with Wynder tobacco tar and has not achieved one instance remotely resembling cancer. These embryonic tissues are very susceptible to carcinogens. However another investigator, Lasnitski (1379), has achieved some results by treating human foetal lung grown in vitro (glass) with tobacco tar. Lasnitski reviewed the experimental lung tumor field and concluded that "there is no experimental proof that human lung (sic) is susceptible to benzpyrene." She therefore applied 3,4-benzpyrene to 176 explants from five foetuses. A 4% solution of 3,4-benzpyrene in acetone was shaken into horse serum and added to the lung tissue culture. Doses used were 1, 4 and 6 mg per ml of medium. The results show that 3,4-benzpyrene directly promotes proliferation of this bronchial epithelium. An increase in the number of cell layers with irregular enlargement of cells and abnormal mitosis was observed and growth of connective tissue and cartilage was suppressed. The author noted that the effects were similar to that of 20-methylcholanthrene on mouse prostate glands. Lasnitski concludes that 3,4-benzpyrene either alone or in conjunction with other compounds in

cigarette smoke "cannot be excluded as a causative agent in human lung cancer."

Lasnitski (3480) has continued such work on human tissue and that of pigs using smoke condensates. Two fractions of cigarette smoke were used on the human tissue, one containing hydrocarbons and the other free of hydrocarbons. Treatment with either fraction caused changes similar to those described in the experiments with 3,4-benzpyrene. Hyperplasia, secretory activity, mitotic abnormalities and variations in nuclear size were more conspicuous in the tissue treated with the hydrocarbon fraction, while glandular hyperplasia and a tendency to squamous metaplasia were more pronounced in those exposed to the hydrocarbon-free fraction. However, the pig bronchus was unaffected by application of 20-methyl-cholanthrene, 3,4-benzpyrene, or three fractions of cigarette smoke condensate in concentrations similar to those which produced changes of a "precancerous nature" in cultures of human foetal bronchus.

IV-C-27

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(iii) Other test animals

All attempts to induce cancer with cigarette tar in animals other than mice and rabbits have proved unsuccessful. Tobacco tars were introduced by Rockey et al. (2643) directly into the trachea of dogs after operations were performed giving direct access to that area. The tar produced prompt metaplastic changes in the mucosa but "nothing suggestive of so-called precancerous alteration was seen". The authors felt this could be the result of a nonspecific reaction to irritation. Continued painting caused no progressive changes but survivors were still under treatment.

Moore and Miller (2996) were unable to produce any cancer in the oral pouch of hamsters after attaching tar-saturated pads to that area. This experiment lasted two years over which each animal was given 8 pads. Tumors did not even arise in the treated animals.

When pure 3,4-benzpyrene powder was applied to the pouches one tumor occurred in 13 months. Salley et al. (3766) gave several reasons for the negative results: after the first few days the tar-saturated pads became diluted by saliva, or that tobacco is not carcinogenic to hamsters' pouches (see also Tabah et al. (1436)).

### 3. EXPERIMENTS WITH REGARD TO THE LUNG AND OTHER SITES

#### a. Inhalation experiments

Attempts to induce lung cancer by the inhalation of tobacco smoke and other aerosols have a long history (280, 1089). Exposure of animals to aerosols other than tobacco smoke will be discussed in detail in the section on Environmental Factors.

In 1936 Campbell (59) exposed mice to exhaust gas and tobacco smoke seven hours a day, five days a week, from age three months until death. The exhaust gas had very little effect on the death rate, body weight and rate of growth, as compared to the control mice, and there was scarcely any difference in tumor development. Similarly, the mice exposed to smoke from Virginia cigarettes did not differ markedly from the controls. Although six more lung tumors were found in the mice exposed to the smoke, the investigator thought this was a function of age. These results were insignificant when compared with the effects previously achieved by Campbell with dust from tarred roads. This dust had caused cancer of the skin and lung tumors in 80% of the experimental animals. Campbell believes that the lung tumors observed in mice are the same as in man despite the lack of metastases. Furthermore, no histological differences existed between the tumors of the experimental and control mice. In the experiments

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) using dust from tarred roads, dust particles were found in the area of the lung tumors.

In 1941, Mertens (283) observed that exposure of mice to cigarette smoke resulted in the development of metaplasia and ulcers in the animals so exposed. No lung tumors were noted.

Lorenz et al. (268) in 1943 also obtained negative results.

) In 1952, Essenberg (113) exposed strain A mice to cigarette smoke (12 cigarettes daily; one per hour). After 14 months, 13 of the experimental and 4 of the control animals were dead. The evidence of lung adenomas in the survivors in the experimental group was 32% greater than in the controls (Note; Strain A is a lung-adenoma-susceptible strain). In 1953, Essenberg conducted a similar experiment (114) to determine the effect of cigarette paper smoke on A-JAX strain mice. He concluded that cigarette paper smoke has little effect on this strain. He also investigated the effect of cigarette smoke on C 57 mice (115). Most of the animals died of pneumonia before lung tumors developed.

) In 1955 (571) and 1956 (928, 928-A), Essenberg et al. continued their studies on inhalation of cigarette smoke and concluded that since cigarette paper smoke and arsenic were ineffective in tumor formation in their experimental animals, the nicotine in the

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cigarettes must be the responsible agent.

Starting in 1954, Passey also exposed mice for most of their life to cigarette smoke. His latest report (4167) made in August, 1958, reported no cancers or lung tumors in rats and hamsters as well as in mice by exposure to strong concentrations of cigarette smoke.

However, Passey noted that the animals exposed to smoke showed evidence of marked constrictions of the peripheral vascular system in general. He stated that the whole of the respiratory tract in a heavy smoker can be subjected to considerable and lasting changes of a generalized nature. These changes may be important in the genesis of cancer and he theorized that there may be no need to invoke the action of any chemical carcinogen.

Peacock (2866), another British investigator, has devised a technique for training animals to receive directly into their buccal cavity cigarette smoke from a manually operated apparatus. He has exposed fowls, pigeons, hamsters, desert rats, Wistar rats and rabbits to smoking three times a week for periods varying from a few months to more than two years. As yet no primary bronchogenic tumors have been observed. One out of seven male Wistar rats developed a small wart at the angle of the

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mouth where the cigarette holders is applied and a benign papilloma of the tip of the tongue was observed in one of the four desert rats which had been smoking for two years and died at the age of 2-1/4 years.

Weller (722) has exposed 132 mice to the smoke from 26 cigarettes a day. The experiment lasted 23 months. While the experimental mice had a higher mortality rate due to increased acute infections and suffered more inflammatory lung disease, they did not differ significantly from the controls in chronic or neoplastic diseases. One primary lung tumor occurred in the experimental group of 132 mice but this was of no significance according to the investigator. The species of mice used was a strain more susceptible to carcinogens and has an incidence of lung cancer similar to man. A study is now underway which will expose rabbits to normal smoke from regular cigarettes (2803-A). Another group will be exposed to cigarette smoke with arsenic added. The investigators plan to let the rabbits live out their life span and will report subsequently.

A series of experiments which have excited considerable interest are those being performed by Leuchtenberger et al. (2573-A). These investigators exposed 275 female CF 1 albino mice in glass chambers to cigarette smoke, starting with one half to one cigarette a day and

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building up to as many as eight. The initial effect was irritation of eyes and nose but this abated quickly. There was some loss of hair and while no exposed mice gained weight a considerable number lost weight. Histological examinations showed that some of the exposed mice had no changes in the trachea or lung, others had suffered from bronchitis with mild proliferative epithelial changes and others suffered from bronchitis with marked, often atypical, proliferative epithelial changes which showed features of cancer in situ similar to those described by Auerbach in the lungs of smokers. The bronchitis observed differed from viral bronchitis. The similarity between the lesions of the mice and those of smokers justified a cautious optimism of the validity of this experimental approach according to the authors. However, they cautioned that further investigation was necessary to see if these changes regressed or continued into cancer.

These authors have reported more recently that mice exposed for two years to 1500 cigarettes have not shown any invasive carcinoma. In mice whose exposures were stopped there was a gradual return to normal tissue and the cytochemical changes also were reversed.

Lupu and Velican (2583) exposed guinea pigs

to the smoke from one-half a cigarette fifteen minutes daily for periods up to eight months and rabbits for periods up to 16 months. Microscopic examination of the lungs of the animals which were killed at various intervals revealed a progressive process of pulmonary sclerosis in all the animals. No lung tumors were reported.

Muhlbock (1029) in 1955 exposed both male and female F-1 hybrid mice (female, C20; male, DBA) to cigarette smoke for two hours daily for two years. The smoke was administered after collection in a human mouth followed by exhalation into the cage or by similar use of a syringe. The test animals showed 79 percent pulmonary tumors (termed in the text as papilloma and in the summary as carcinoma) compared with 31 percent for the controls. No substantial differences were observed between the sexes in respect to tumor incidence.

It may be noted here that the DBA strain, as described by Shimkin (1089), usually shows 5% spontaneous pulmonary tumors (adenomas) and thus the hybrid mouse described by Muhlbock must be substantially different from the DBA strain. Muhlbock stated that the controls showed 31% spontaneous pulmonary tumors. Muhlbock did note, however, that the tumors (whatever type they were) were not similar to the bronchial carcinoma in man.

IV-C-34

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b. Direct application

Other methods besides inhalation have been used to attempt to induce lung tumors in experimental animals.

Dellaporta et al. (2759) in one such experiment placed known carcinogens and cigarette tar separately in colloidal suspension of 1% in gelatin and then dropped directly into the tracheal-bronchial tree of Syrian golden hamsters. Cancers were induced in the trachea, larynx and major bronchi by repeated feedings of the known carcinogens. Not even early epithelial changes were caused by the cigarette tar. The authors play down this result as having no significance with regard to the human lung cancer problem.

Blacklock (2124) is studying the inoculation of tobacco tar into the lungs of rats and guinea pigs exposed by thoracotomy, the animals being killed at regular intervals after inoculation. So far he has found that if tobacco tar enters a bronchus, it soon produces a squamous metaplasia of the bronchial mucosa, sometimes with papillomatous change. It is too early for a malignant change to have occurred. Town soot has also been employed alone and in conjunction with tobacco tar

and the combination has produced squamous metaplasia, although soot alone has not. These changes correspond to those observed by Auerbach. Especially noted are the changes in the lungs of guinea pigs since these animals are regarded as refractory to most carcinogens.

Blacklock has stated:

"So far as we know, malignant tumors have not been produced in the lungs of animals by any known carcinogen owing to the technical difficulty of applying such substances directly to these organs\* \*\*. Indeed it is not known if the highly specialized tissue of the lungs will respond like the skin in a neoplastic manner to any known carcinogen."

Blacklock was able to produce sarcomas and carcinomas in the lungs of rats by injection of 3,4-benzpyrene or 20-methylcholanthrene but not from the tar collected from four cigarettes mechanically smoked and injected into the lung (10 rats). A carcinoma and a sarcoma were produced in eight rats each of which was injected with the tar from four cigarettes in conjunction with dead tubercle bacilli. No tumors were found in the lungs of several groups of controls which included one group treated with the dead tubercle bacilli in olive oil.

Blacklock refers to Jensen (Z. Krebsforsch., 7, 45 (1909)) who observed sarcoma in two rats which had been inoculated with acid-fast bacilli from a pseudo-tuberculous enteritis of the ox.

IV-C-36

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## D. CHEMICAL STUDIES ON TOBACCO PRODUCTS

Plaintiffs may be expected in pretrial proceedings to specify, or at trial to have witnesses testify, as to carcinogens present in cigarette tobacco, in cigarette smoke, in cigarette paper, or in tobacco condensates (tar). This has already been done in Pritchard v. Liggett & Myers Tobacco Co. where plaintiff named the following:

Carcinogens, cited in 1959 by Wynder (3525):

3,4-benzpyrene	considered potent
1,2,5,6-dibenzanthracene	carcinogens
3,4-benzfluoranthene	(see also (3858,
10,11-benzfluoranthene	4107))
1,2-benzpyrene	
1,12-benzoperylene	considered very
1,2-benzathracene	weak carcinogens
chrysene	

Parenthetically, tobacco carcinogens reported by others but not mentioned by Wynder are:

3,4,9,10-dibenzpyrene	- strong carcinogen
1,2,3,4-dibenzpyrene	- probable "
9,10 dimethylbenzanthracene	- very strong carcinogen
3,4-benzphenanthrene (benzo(d)phenanthrene)-	very weak carcinogen
3,4,8,9-dibenzpyrene	- strong carcinogen
1,2,7,8-dibenzfluorene	- questionable carcinogen

Such specification, if substantiated qualitatively and quantitatively, would lend support to affirmative animal experiments and epidemiological studies (see other sections of this report).

This section reviews the major literature on the subject in chronological fashion to lay the basis for cross-examination of plaintiffs' experts, or possible pretrial demands for admissions.

At the outset it should be noted that the following factors influence the composition of tobacco smoke:

rate of burning (duration, frequency  
and volume of puffs per minute)

air supply

temperature of glowing coal

length of unsmoked butt

moisture content of cigarette

Experiments vary as to the above, and results are not consistent. (See Wynder et al. (1134-B)). In addition, results vary as to whether whole tobacco leaf is smoked, extracts are removed from leaf for experimentation, or smoke is condensed or distilled.

Wynder (3525) refers to a number of other articles indicating identification of 3,4-benzpyrene in tobacco smoke condensate. With the exception of Roffo's 1939 article (363), all Wynder's references are to 1955 or later publications. Roffo produced skin cancers on rabbits' ears by application of tobacco tars prepared by heating tobacco at 120° C

for 6 days and collecting the pyrolysate below and above 380° C separately - a procedure obviously not comparable to the human smoking process.

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IV-D-3

## 1. POLYCYCLIC HYDROCARBONS

Cooper et al. (81) took neutral extract of condensed tobacco smoke and, by absorption spectrophotometry, and fluorescence spectrography, confirmed Cooper and Lindsey's results (published in 1953) as to the presence of anthracene and pyrene, non-carcinogenic hydrocarbons (903-A). They also found 1 microgram (1 part per million) of 3,4-benzpyrene per 100 cigarettes. They remark that a person smoking two packs daily (inhalation of 150 micrograms of 3,4-benzpyrene in a year) inhales 50 micrograms less than breathed from average urban atmosphere. The authors point out a weakness in this argument is that inhaled air is partially filtered in nostrils, which is not the case with inhaled cigarette smoke. Cooper and Lindsey (80) also reported presence of 3,4-benzpyrene and other polynuclear aromatic hydrocarbons in cigarette paper smoke.

In 1955, Cooper and Lindsey (903-B), with improved apparatus but the same techniques, found 3,4-benzpyrene ("minimal traces" according to Kuratsune (986), and 1,12-benzoperylene and traces of other hydrocarbons not yet cited by a plaintiff. They



stated:

"...no specific carcinogen has previously been shown in such smoke... 1:12-Benzperylene...(is) only feebly (carcinogenic)."

Wynder and Wright (1137-B) by testing various fractions of tar, estimated that there can be no more than one part per million of 3,4-benzpyrene in the total condensate. They state:

"...We feel that as yet unestablished carcinogens or co-carcinogens are in tobacco tar, since the concentration in which benzpyrene seems to be in cigarette tar is insufficient to account for the observed carcinogenic activity to mouse epidermis."

Lam (989-A) of Denmark isolated aliphatic hydrocarbons from cigarette butts, subjected them to pyrolysis at about 800° C and spectrophotometry, and found 3,4-benzpyrene, 1,2-benzpyrene, naphthalene, pyrene and anthracene in the pyrolysate.

Seelkopf (705-A) in 1955 reported 3,4-benzpyrene, anthracene and naphthalene in cigarette smoke condensate. Lettre and Jahn (993) in 1956 reported anthracene, pyrene, 1,2-benzanthracene, 1,2-benzpyrene and 3,4-benzpyrene in cigar butts.

In 1956, Bonnet and Neukomm (882) found 2.2 micrograms of 3,4-benzpyrene in the smoke from 100 cigarettes, 10.2 micrograms of anthracene; 9.7 of

pyrene; 8.0 of 1,2-benzanthracene. They also claim 1 microgram of 3,4,9,10-dibenzpyrene (apparently a potent carcinogen (1378, 2569, 3370, 4194)) in the smoke from 100 cigarettes.

Lyons (1007) found 7.4 micrograms of 3,4-benzpyrene in the smoke from 500 cigarettes, both by fluorescent spectrography and absorption spectrophotometry. He also found 1 microgram of 1,2-benzanthracene in the smoke from 500 cigarettes. Both are referred to as having "semi-quantitative significance". He does not report 1,2-benzpyrene.

Wynder and Wright (1137) stated anthracene, pyrene, perylene, fluoranthene, chrysene, 3,4-benzpyrene to be present in neutral cigarette smoke condensate by spectrographic analysis. They also burned cigarette paper in bulk, fractionated the tars and then had them paper chromatographed. They stated:

"...Only the paper burned unrealistically in bulk shows the presence of benzpyrene above the detectable level." (1 to 10 parts per million (ppm)).

Cardon, et al. (1328), by ultraviolet fluorescence and absorption spectra, found 3,4-benzpyrene in smoke of cigarette paper, tobacco and cigarettes, in relatively small quantities.

Kosak, Swinehart and Taber (583,980-A) by chromatographic and absorption spectra methods, made negative analysis of smoke extract for benzo(a)pyrene (i.e., 3,4-benzpyrene). It should be noted that in a later paper, Orris, Van Duuren, Kosak, et al. did find, 3,4-benzpyrene (3179).

In 1956, Kuratsune (986) investigated the presence of 3,4-benzpyrene in various materials and found none in cigarette smoke, but did find it in soots of coal and wood, combustion products of gasoline engines, charred biscuits and charcoal briquettes. Some was found in cigarette ends and ashes and the conclusion was reached that "small amounts of benzpyrene are produced by smoking, but that only a very small part...thus formed appears in the inhaled smoke" due to absorption in the cigarette end, escape in uninhaled smoke or destruction in burning zone. He later found small amounts (200-440 micrograms per kilogram) in coffee roasting soots (2568-A).

Gilbert and Lindsey (1654), supported by Kennaway, followed up prior experiments (dealing with presence of certain polycyclic hydrocarbons in cigarette smoke) with an experiment to determine content of these materials in stubs and ash of cigarettes.

They found 0.5 micrograms of 1,2-benzanthracene and 0.3 micrograms of 3,4-benzpyrene (also others not yet cited) in the ash of 500 cigarettes. The following is a comparison with prior experiments; the value being micrograms per 500 cigarettes:

	<u>smoke</u>	<u>stubs</u>	<u>ash</u>	<u>total</u>
3,4-benzpyrene	4.0	10.0	0.3	14.3

These investigators also conducted pipe smoking experiments (1654-A).

Cooper and Lindsey identified 3,4-benzpyrene and 1,12-benzoperylene in cigarette smoke.

Latarjet et al. (1163) found 1.2 micrograms of 3,4-benzpyrene per 100 French cigarettes by similar but improved methods, and 3 micrograms from wrappers (cigarette paper) of 100 cigarettes.

In a speech before the Third National Cancer Conference in 1956, Wright (1299) described experiments demonstrating that cigarette paper burned in a manner simulating its combustion on a cigarette (that is, in cylindrical form) did not yield 3,4-benzpyrene. Only when the cigarette paper is burned in bulk is 3,4-benzpyrene formed. This combustion in bulk was the method used by several authors, Cardon et al. (1328), Cooper and Lindsey (80), etc.

In 1957, Lyons and Johnston (2585-A)

investigated the neutral fraction of condensate from British cigarettes, and with repetitive absorption chromatography revealed the presence (in approximate concentration levels of less than 2 ppm of whole smoke condensate) of 1,2-benzpyrene; 3,4-benzpyrene; chrysene and 1,2-benzanthracene (traces); 1,12-benzoperylene; 3,4,8,9-dibenzpyrene; 11,12-benzfluoranthene (not a carcinogen); and 1,2,7,8-dibenzfluorene. But they did not find 3,4,9,10-dibenzpyrene (as did Bonnet and Neukomm (882)). All those claimed to have been found are carcinogens, except as indicated.

Wynder and Wright (2054-E) cited unpublished work in which Wynder collaborated with Graham and Croninger, the investigations of Sugiura (1289), as well as work with Graham (475,800-B) as demonstrating carcinogenicity of tar to skins of "several strains of mice". For this reason, they stated, it was of interest to determine the nature of the carcinogens responsible. They noted that "preliminary data" were published elsewhere (citing Wynder and Wright (1137, 1137-B)), but that they here report "initial results". They employed chemical fractionation, molecular distillation and ion-exchange, and found 1 ppm of 3,4-benzpyrene and suggestive evidence of

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chrysene and 3,4-benzfluoranthene and other hydrocarbons not yet cited by plaintiff.

The following comments by Wynder and Wright (2054-E) with regard to extrapolation to humans are worthy of note:

"The purpose of this investigation has not been to prove that tobacco smoking causes cancer in man. Such proof can come only from combined statistical, clinical, and epidemiological studies on man. Because such studies have established a relationship between tobacco and several types of human cancer, the present investigation was initiated to determine the specific carcinogenic substances in tobacco. Obviously, such a study can determine these factors only for a specific experimental animal. It remains to be established whether such factors, once found, are also responsible for cancer formation in man."

They go on to state that one can only "assume" that a carcinogen responsible for cancer in test animals is also responsible for cancer formation in man.

Noting that traces of 3,4-benzpyrene have been spectroscopically determined by a number of investigators to be among the carcinogens in cigarette tar (citing Cooper and Lindsey; Latarjet et al.; Lyons; and themselves, all in 1955 or subsequently), they state further:

"Cigarette tar used in this study contained between 1 and 2 p.p.m. of benzpyrene. One does not know what level of continued

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exposure may be carcinogenic to man. We have demonstrated experimentally, however, that 0.0001 per cent or even 0.0005 per cent benzpyrene in acetone will not produce any tumors in the present experimental mouse or rabbit groups." [Emphasis supplied. Authors cited an article by Wynder, Fritz and Furth on dosage levels (2448).]

Thus, there is conclusive proof that the animal results cannot be solely due to the benzpyrene content of tobacco \* \* \*

They also discussed arsenic (35 ppm) to which Leitch and Kennaway (255) found the skin of mice to be resistant. They cited Cooper and Lindsey as identifying traces of 1,2-benzanthracene and Wynder and Wright as having found "suggestive evidence of other polycyclic components" which they state "appear to be present in significantly lesser concentration than their carcinogenic threshold."

After citing other suggestive traces, they state:

"There exists, therefore, so far no evidence that a single known carcinogen in condensed cigarette tar can account for the established carcinogenic activity in mice and rabbits. It remains to be ruled out, of course, that these materials together or with the support of unestablished carcinogens or cocarcinogens may produce the observed effects." p. 269

In their summary, they repeat:

"The benzpyrene content of the total tar as well as of the active fractions is far too low to account alone for the positive [animal] results. So far, no carcinogens have been identified in large enough quantity in tobacco tar or its fractions to account for the observed activity. While a summation

effect of several substances remains a possibility, it is more likely that carcinogens not yet identified may be the most important ones in tobacco tar. Current efforts are directed toward their identification." [Emphasis supplied.]

In connection with the theory that small amounts of different carcinogens might exert a concerted effect, Greenstein (142) stated:

"When a mixture of two hydrocarbons of nearly similar molecular configuration, one of which is actively carcinogenic and the other weakly carcinogenic, is applied to the skin of mice, the carcinogenic effect is apparently weaker than when the stronger agent is applied alone [584]. \* \* \* It would appear that the weaker agent, acting in competition at critical physiological sites within the animal with the stronger agent in the mixture, reduces the effect of the latter."

He also refers to Riegel et al., Cancer Research, 11, 301 (1951), in which it is stated:

" \* \* \* simultaneous painting of 20-methylcholanthrene and 1,2,5,6-dibenzfluorene delayed skin carcinogenesis in mice beyond the period characteristic of methylcholanthrene alone, but chrysene, fluorene, and 1,2,7,8-dibenzfluorene had no effect when mixed with the more active carcinogen.

Aromatic polycyclic hydrocarbons in various combinations were tested for carcinogenic activity in the subcutaneous tissues of C57Bl mice. Three strong carcinogens tested with a medium strength chemical (1,2-benzanthracene) caused, variously, summation effects or no effect. A strong carcinogen (1,2,5,6-dibenzanthracene) did not summate with a weak agent (chrysene).

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Chemically related but non-carcinogenic compounds (anthracene, phenanthrene) added to a strong carcinogen (1,2,5,6-dibenzanthracene) did not affect the tumor yield. Doubling the amount of each of two strong carcinogens increased the tumor yield over either alone."

Rand and associates (2358) gave historical treatment to certain animal experiments citing Roffo in 1936; Sugiura in 1940 (1 cancer in 159 animals tested); Wynder et al. (475) in 1953; Cooper, Gilbert and Lindsey in 1954; Latarjet in 1956; as well as his own work. Beginning with the Cooper experiment in 1954, each one cited above found the presence of 3,4-benzpyrene in the tar of both the cigarette and the paper. Kosak (1134-B), citing Cooper and Lindsey's "preliminary" identification of 3,4-benzpyrene in 1954, refers to the work of others who failed to detect it during the period 1932 to 1954.

In 1958, Wynder, Wright and Lam (2722-A, 3372-A) found that tobacco extracts pyrolyzed at above 800° C formed carcinogens, but in lesser amounts at lower temperatures. Different puff volumes affected total amount of tar, but not the carcinogenic constituents on a gram to gram basis. Lam (989-A, 989-B, 1763) had previously conducted similar experiments.

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Van Duuren (2908) (listed as a witness in the Lartigue case) conducted an investigation of the chemistry of cigarette smoke condensate and positively identified 3,4-benzpyrene, 1,2-benzpyrene and 1,12-benzoperylene and others not yet cited by plaintiffs (see also (2695)).

In a later study (3213), he also found chrysene (a weak carcinogen cited by Pritchard), 1,2,5,6-dibenzanthracene (a strong animal skin carcinogen cited by Pritchard), and a benzfluoranthene (not the 3,4-benzfluoranthene cited by Pritchard).

He stated:

"The carcinogenic hydrocarbons found so far do not by themselves appear to be present in sufficient concentration to account for the observed activity \* \* \*."

He noted that there are many possible promoting agents in tobacco tar and that other carcinogenic components as yet unknown may be present. Also Van Duuren reported benzo(c)phenanthrene (a weak carcinogen) and traces of 3,4,9,10-dibenzpyrene (a strong carcinogen). He found 0.002 micrograms of 3,4,9,10-dibenzpyrene in the smoke of 100 cigarettes compared to 1 microgram reported in 1956 by Bonnet and Neukomm (882) and not found by any other investigator to date.

Orris et al. (3179) compared the carcinogenic activity and content in 3,4-benzpyrene, 1,2-benzpyrene and pyrene of cigarette smoke condensate obtained by Wynder's technique with that obtained by the New York University technique and found three to four times more polycyclic hydrocarbons and over two times greater carcinogenic activity for the Wynder tar.

Pietzsch (3185) reported the following carcinogenic hydrocarbons in cigarette smoke: 1,2-benzanthracene, 1,2,5,6-dibenzanthracene, 9,10-dimethyl-1,2-benzanthracene, 1,2-benzpyrene, chrysene, and 3,4-benzpyrene.

Lyons (2991) reported 1,2,3,4-dibenzpyrene to the extent of 1.6 micrograms per 100 cigarettes (smoke). This he claims to be a carcinogen of considerable potency. (In the opinion of some, Lyons' identification of 1,2,3,4-dibenzpyrene is open to question.)

Bentley and Burgan (3062, 3062-A) reported 4.9 micrograms of 3,4-benzpyrene per 500 cigarettes (smoke).

Ahlmann (3051) reported chrysene, 1,2-benzpyrene, 3,4-benzpyrene and 1,12-benzoperylene,

and possibly 6,7-cyclopenteno-1,2-benzanthracene. They did not find 3,4,9,10-dibenzpyrene.

In 1958, Kennaway and Lindsey (2822) reviewed the composition of tobacco and tobacco smoke with particular reference to carcinogens and discuss the issue of lung cancer causes. They concluded:

"This summary of existing knowledge of possible exogenous factors in the causation of lung cancer demonstrates the need for fuller chemical investigation of tobacco, tobacco smoke and town air."

A 1959 article by Wynder (3525) is of general significance as well as of use in preparation for his cross-examination. He started off by saying the sum total of evidence linking smoking to cancer of the respiratory tract is based on different types of evidence:

1. "presumptive" (hardly evidentiary)
2. epidemiological
3. pathological
4. animal
5. chemical

and all demonstrate smoking to be a carcinogenic factor. He then purports to "evaluate" contributions that laboratory research is making. He stated:

"The importance of laboratory work is not to prove that smoking is a

cause of cancer in man. Such proof can only come from human epidemiological investigations. Laboratory research can, however, contribute to, and give a logical explanation for, the human findings. Just as an animal experiment cannot disprove that a given factor causes cancer in man so, by itself, an experiment cannot prove a given agent to be carcinogenic to man."

According to him the aim of chemical and biological experiments is to identify and reduce or remove specific agents. In so doing "we can only assume" that the agents responsible for activity in animals are also responsible for human activity. Although it cannot be proved, by reason of the similarities for tumor growth in animals and man, the assumption of the connection stands on a "firm foundation".

Typical of Wynder is the following non sequitur:

"... In general, it would be advantageous to use the type of tissue similar to the one involved in man. In view of these considerations, the subcutaneous tissue of mice would be a less useful site because it does not yield epithelial tumours and also because it has been shown to be quite sensitive to a large variety of substances.

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On the other hand, the lungs of mice would not represent a good test organ, since, even upon inhaling high doses of potent polynuclear hydrocarbons, it has been difficult to produce lesions in the bronchus in mice. The skin, on the other hand, is a satisfactory site not only because of ease of application, but also because it represents a type of tissue similar to the epithelial tissue of the respiratory tract. [Emphasis supplied.]

Wynder continued:

"An important factor when testing a product to which man is exposed is to test this product under a condition similar to that under which man is exposed. Thus we should smoke tobacco in a manner simulating human smoking habits, and should not distill the tobacco smoke in a closed container. Another important principle is that, when testing a substance suspected to be only weakly carcinogenic, the substance should be applied in maximum concentration over a maximum period of time. With these considerations on methodology we shall review the actual experiments already completed." [Emphasis supplied.]

Wynder then discusses animal studies and says that it is most difficult to produce bronchogenic lesions by inhalation experiments. He cited Campbell and Essenberg as having produced pulmonary adenomas in susceptible mice by inhalation experiments (Campbell in 1936, Essenberg in 1955), but stated that Lorenz (1943) obtained negative results. He also cites the Leuchtenberger experiments.

Turning to skin studies, Wynder stated that no study of this type was done with condensed tobacco smoke until 1953 at which time he and his associates published

their first report, but concedes that Hamer and Woodhouse as well as Passey in 1956 and 1954, respectively, reported negative experiments. He also cites Roffo's series of production of cancer in rabbit ears with a tobacco smoke distillate but concedes "it could be argued that this distillate represented a variance from the tobacco smoke condensate". It may be noted here that Cottini and Mazzone (82) applied a 1% solution of 3,4-benzpyrene to the skin of man for 120 days without observing cancers, and the changes that did appear regressed upon discontinuance of the applications.

Turning to chemical data, Wynder noted that many have identified 3,4-benzpyrene in tobacco smoke but that "it is generally realized, of course, that this amount of benzpyrene is not sufficient to account by itself for the carcinogenic activity of the total tar". He listed a number of polycyclic hydrocarbons, the first eight of which are cited by Pritchard in answer to interrogatories. Wynder says that there obviously remain other polycyclic hydrocarbons still to be identified.

\* \* \* \*

Gilbert and Lindsey (2524) conducted a pyrolysis study on the major components of tobacco. They found 1,2- and 3,4- benzpyrene as well as 1,2-benzanthracene in the pyrolysates. The compounds studied, presumably constituting some 62% of flue-cured tobacco, were as follows: cellulose, lignin, pectin, starch, sucrose, glucose, fructose, malic acid, citric acid and oxalic acid. The polycyclic hydrocarbons obtained in addition to those mentioned above were: acenaphthylene, fluorene, anthracene, pyrene, fluoranthene, 3-methylpyrene, anthanthrene and coronene.

Neukomm and Bonnet (2606, 2999) discussed the carcinogenic polycyclic hydrocarbons in cigarette smoke. Specifically mentioned were 3,4-benzpyrene and 1,2-benzanthracene. They also discussed the possible cocarcinogenic activity of polymeric material in the smoke.

At two meetings held in 1959, Hoffman and Wynder (3858, 4107) described the isolation of crystalline 3,4-benzpyrene from cigarette smoke. The compound was identified on the basis of standard chemical procedures, e.g., melting point, mixed melting point, etc. They also listed several other polycyclic hydrocarbons determined by them: 3,4-benzfluoranthene, 10,11-benzfluoranthene, 11,12-benzfluoranthene, and benzo[mno]



fluoranthene. The 3,4- and 10,11-benzfluoranthene have been shown to be carcinogenic. They noted that of the 17 higher polycyclic hydrocarbons identified by them in cigarette smoke, eight are known to be carcinogenic to mouse epidermis.

Bailey (4026) found as much 3,4-benzpyrene in one kilogram of smoked trout and mutton as in the smoke from 350 cigarettes.

Cardon (3246) found 12 micrograms in the smoke from 400 cigarettes; a value which checks with that reported from the Rand group previously (13 micrograms). An improved isolation technique was reported also.

Rayburn et al. (3190) found that hexane soluble material had no effect on the quantity of polycyclic hydrocarbons absorbing at 385 mm. in cigarette smoke. These results are in disagreement with the more recent findings of Bonnet and Neukomm (3556-A) who found that hexane extraction reduced the 3,4-benzpyrene by 50 to 70%. Other polycyclic hydrocarbons were also reduced substantially.

Clerno (4056) disagreed with Wynder on the importance of the polycyclic hydrocarbons in cigarette smoke, and suggested that irritants such as the phenols, etc., could sensitize the smoker's lungs to carcinogenic

attack.

Lindsey (3700-A) supposedly confirmed the suggestion of Doll et al. (3419) and Hammond (3132-A) that differences in butt length in cigarette smoking might result in substantial difference in the amount of carcinogenic hydrocarbons inspired. The data for 1,2-benzanthracene and 3,4-benzpyrene follow in micrograms:

<u>Hydrocarbon</u>	<u>Smoke</u>		<u>Butt extract</u>	
	<u>15 mm.</u>	<u>35 mm.</u>	<u>15 mm.</u>	<u>35 mm.</u>
1,2-benzanthracene	14.0	8.0	8.5	14.0
3,4-benzpyrene	3.0	0.7	2.0	3.0

Thus, a cigarette smoked to a butt length of 35 mm., for example, has less 3,4-benzpyrene in the smoke and more of this compound retained in the butt than in the case of a cigarette smoked to a 15 mm. butt.

Lam (3477) in 1959 investigated the mechanism of formation of polycyclic hydrocarbons in cigarette smoke by pyrolysis of tobacco paraffins. Inclusion of 1,2-benzanthracene in small amounts in the pyrolysis of tobacco paraffins increased the amounts of 3,4-benzpyrene, suggesting a free radical mechanism for formation of at least some of the polycyclic hydrocarbons.

Although in some instances the evidence is not too substantial, the following list represents most of the polycyclic hydrocarbons reported in cigarette smoke

(those underlined have or are suspected to exhibit some degree of carcinogenic activity):

acenaphthene

acenaphthylene

anthanthrene

anthracene

azulene

1,2-benzanthracene

3,4-benzfluoranthene

5,6-benzofluoranthene

10,11-benzfluoranthene

11,12-benzofluoranthene

benzo[mno]fluoranthene

1,2-benznaphthacene

1,2-benzfluorene

2,3-benzfluorene

1,12-benzoperylene

3,4-benzphenanthrene

1,2-benzpyrene

3,4-benzpyrene

chrysene

coronene

5,6-cyclopenteno-1,2-benzanthracene

6,7-cyclopenteno-1,2-benzanthracene

1,2,5,6-dibenzanthracene

1,2,7,8-dibenzfluorene  
1,2,7,8-dibenznaphthacene  
1,2,3,4-dibenznaphthacene  
2,3,6,7-dibenzphenanthrene  
1,2,3,4-dibenzpyrene  
3,4,8,9-dibenzpyrene  
3,4,9,10-dibenzpyrene  
3',4'-dihydro-3,4-benzpyrene  
9,10-dimethyl-1,2-benzanthracene  
1,8-dimethylnaphthalene  
2,5-dimethylphenanthrene (?)  
fluoranthene  
fluorene  
3-methyl-1,2-benzanthracene  
9-methyl-1,2-benzfluorene  
8-methylfluoranthene  
8-methylfluorene  
9-methylfluorene  
2-methylnaphthalene  
9-methylphenanthrene  
1-methylpyrene  
3-methylpyrene

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4-methylpyrene  
naphthalene  
1',2'-naphtho-1,2-fluorene  
2',3'-naphtho-3,4-pyrene  
perylene  
phenanthrene  
pyrene  
1,2,3,4,5,6-tribenzanthracene

Several methylated derivatives have also been reported but since the precise position(s) of the methyl groups were not described, we have omitted these from our list. Bentley and Berry (3544) have presented an excellent summary of all of the constituents of tobacco smoke known at the beginning of 1958.

In summary, we have the following material (previously described in detail) for cross-examination:

Until 1954 no one had identified polynuclear aromatic hydrocarbons suspected to be of possible carcinogenicity in cigarette smoke or condensate. Early reports referred to carcinogenic hydrocarbons without specification as to their structure. These articles gave no evidence to substantiate the identification.

It was not until the mid-1950's that improved methods were available. Ultraviolet absorption curves were not presented until 1956. Cardon and Rand (1328) did so in that year. These represented impure samples. Unavailability of pure samples precluded chemical identification by melting points, elemental analyses, formation of derivatives, etc. In 1957-8 absorption curves were confirmed by chromatographic behavior.

It was not until 1955 that 3,4-benzpyrene was identified in cigarette smoke (81, 903-B). Wynder conceded that "the concentration in which benzpyrene seems to be in cigarette tar is insufficient to account \* \* \*" for positive mouse experiments (1137-B) (see also van Duuren (3213)). There are variances in the amount of 3,4-benzpyrene found by investigators. Kosak had a negative analysis for 3,4-benzpyrene in 1956 (583, 980-B) and a positive one in 1958 (3179).

No one knows what, if any, level of continued exposure to 3,4-benzpyrene may be carcinogenic to man.

Other hydrocarbons are cited by Wynder as present by "suggestive evidence" in "significantly lesser concentration than their carcinogenic threshold".

Re summation effect; Greenstein and others do not accept the proposition that a combination of carcinogens have a summation effect.

Sources of carcinogenic hydrocarbons other than cigarette smoke will be described in detail in the section on Environmental Factors.

## V. ENVIRONMENTAL FACTORS IN LUNG CANCER CAUSATION

### A. ATMOSPHERIC POLLUTION

#### 1. INTRODUCTION

This section will discuss environmental factors in the causation of lung cancer; will outline the major theses in that field as revealed by the available scientific literature and will summarize the arguments indicating that air pollution may be responsible for lung cancer. In view of the plethora of literature on the subject of environmental factors in the etiology of lung cancer, much of it repetitive or in the nature of a review of the work of others without any original work on the part of the author, we have not attempted to include all or even substantially all of the papers in the field in our discussions herein but have tried to limit ourselves to the more important ones.

We adopt the following definition of man's environment: the sum of all the external conditions and influences affecting his life. This section will deal with those conditions and influences, except tobacco smoke (see preceding sections), which have been seriously advanced as causing or contributing to the high incidence of lung cancer. The same type of evidence is used to incriminate both tobacco smoke and air pollutants. They are often considered to be joint agents in the etiology of lung cancer.

V-A-1

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The environmental factors dealt with herein are divided as follows:

1. Atmospheric Pollution
2. Occupational Exposure
3. Geographical Factor
4. Socio-economic Factors

At the outset we want to emphasize that we do not propose to do an advocate's job of exculpating tobacco and incriminating environmental causes of lung cancer. We shall try to lay out not only those arguments which point to environment as an etiologic factor in lung cancer, but those arguments which have been advanced as detracting from the role of environment regardless of whether or not they appeal to us as being well-founded. At the same time we have tried to anticipate likely developments in cancer research so as to avoid luring the reader into taking a position which in all probability will shortly be indefensible. In summary, we have avoided insofar as possible the expression of personal opinion on the etiology of lung cancer in the belief that such opinion is irrelevant in the first place, and that in the second place a biased view will fail to produce the full panorama of the literature which is essential to the appreciation of a field characterized

not by certainty or logic but by confusion.

In 1955 Hueper reviewed the epidemiological, medical and experimental data available on exogenous respiratory carcinogens. He concluded that it is "unlikely" that cigarette smoking is a major factor in lung cancer and its phenomenal rise in frequency, and that much of the evidence implicates occupational or industry-related factors, i.e. soot, coal tar and pitch, petroleum oils, gasoline and diesel engine exhaust. Subsequently, however, in his deposition in Lowe vs. R. J. Reynolds Tobacco Company in 1957 and in a paper published about the same time he expressed himself differently as to the role of smoking (although hewing to his earlier view as to industry-related factors):

"These observations, considerations and interpretations [concerning environmental factors other than smoking]\* \* \*do not favor the concept that the great majority of lung cancers, particularly those in men, are caused by excessive cigarette smoking. The epidemiologic evidence concerning this factor, on the other hand, is sufficiently impressive to attribute to cigarette smoking a definite, while less direct or indirect, role in the production and rise in frequency of cancers of the lung.

\* \* \* \* \*

This assessment of the probable role of cigarette smoking in the lung cancer problem, however, in no way weakens the fact that excessive cigarette smoking is an unhealthy habit for this and other reasons, and therefore should be discouraged."

V-A-3

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The following summarizes some of the considerations leading Hueper (1707-C) and others to suspect industry-related factors in the etiology of lung cancer:

1. The rise in lung cancer rates started before cigarette smoking became widespread; and no consistent relation exists between cigarette consumption and lung cancer rates in different countries. For example, the lung cancer death rate for England and Wales is twice that of the United States, while the per capita consumption of cigarettes in the United States is 30% higher. This argument is met by the anti-tobacco forces with the attempted explanation that the British smoke their cigarettes to a much shorter butt length (970-B). This argument has been advanced by Doll et al. (3419) and Hammond (3132-A) and was supposedly confirmed by Lindsey (3700-A) in his study on polycyclic hydrocarbons (See Chemical Studies of Tobacco Smoke). Another such example in support of Hueper (1707-C) is the finding of Eastcott (923) that emigrants from Great Britain settling in New Zealand have more lung cancer than natives smoking just as much.

2. The progressive rise in frequency of lung cancer since 1900 has been accompanied by an increasing pollution of the atmosphere with industrial effluents, some of which have been demonstrated to be carcinogenic.

3. Hueper believes that the outstanding feature of the increase in lung cancer is its irregularity as to time of onset, degree of rise, progression rate, sex distribution, and annual and relative increase in tobacco consumption in different countries and regions or communities, and its consistent association with the degree of population density, industrial activities, urban and rural areas and population groups, and the industry-related pollution of the atmosphere with known carcinogens. He illustrates this proposition by turning to the increase in lung cancer deaths among Danish males, first noticeable in 1930, and restricted at that time to males residing in Copenhagen; it was not until 10 years later that an increase was noted for males in rural and small town areas of Denmark (cf. Clemmesen et al., infra).

Another illustration given by Hueper is a study of Pittsburgh respiratory and skin cancer rates, which showed that certain highly polluted downtown areas had rates for such cancers practically twice for men living elsewhere in the city. He reminds us that many occupational agents, such as coal tar, petroleum oils, arsenicals and radioactive substances, which cause cancer of the skin, also elicit lung cancer on inhalation.

V-A-5

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4. While as a general rule urban and industrialized and densely populated areas have definitely higher lung cancer rates, there are marked differences in this respect among communities of the same size and type, as well as exceptions to the rule. Hueper observes that whatever factors were introduced into our environment 75 years ago and caused a rise in the lung cancer rate in the last 50 years did not become active everywhere at once, although males were usually most strongly affected.

5. The obvious factor or factors in the human environment fulfilling the foregoing epidemiologic conditions are those related to industrialization, but some writers have advanced cigarette smoking as the appropriate agent. Hueper questions the scientific value of some of the data used to establish the position of some (i.e., Doll and Hill (103, 918-D), Hammond and Horn (2534-A, 2534-B), Kreyberg, Haenszel and Shimkin) that urban-rural disparity is attributable completely to heavier smoking by urban populations; he also believes that the irregular pattern of lung cancer for various regions and population groups associated with exposure to industry-related air pollutants of widely different types and degree practically precludes singling out a single factor as being responsible for

the wide variations in incidence rates. In this connection he adverts to the fact that lung cancer is not a disease entity by itself but is a group of diseases with different and distinct causal factors, so that it is unwise to embrace sweeping conclusions with regard to the causal relation of a single factor such as smoking.

Hueper comments effectively on the estimate of Stocks and Campbell (1104-A) that 50% of the lung cancers observed by them in Liverpool and surrounding areas are due to cigarette smoking and three-quarters of the balance to an urban factor. This estimate, he writes, is heavily biased by the arbitrary assumption that the alleged 3,4-benzpyrene content of cigarette smoke is 12 times as effective in eliciting lung cancers as 3,4-benzpyrene in the atmosphere. At this point we might call attention to more recent work of Kotin et al. (982, 2561-B, 3474) which purports to show that there are present in the atmosphere potential human carcinogens other than 3,4-benzpyrene, viz.: oxidation products of aliphatic hydrocarbons, which can be created by internal combustion engines, and which have elicited pulmonary carcinomas in a tumor-resistant strain of mice. There is no evidence to date that such compounds are present in cigarette smoke; Kotin states, however, that

V-A-7

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they are a concomitant of industrialization (3474).

6. Hueper singles out for caustic comment the theory that the increase in lung cancer has been greater among males, that the increase paralleled the greater use of cigarettes by males, and that hence there is a causal relation. He argues that this relation can be found only by ignoring the considerable fluctuations found in the sex ratio in different countries, among different population groups, at different times. And he makes the telling point, also stressed by Kotin (982), that women have not been exposed to the same degree as men to industry-related air pollutants. He further argues that whenever the type and degree of contact with respiratory carcinogens for occupational or environmental reasons becomes equalized, the sex ratio tends also to equalize; as examples he gives asbestosis cancer of the lung and domestic soot cancer of the lung in Mexican women. Indeed, there is some evidence, he says, that the male-female ratio may be as high as 16:2 even though women are heavy smokers.

7. During the past few decades increasing amounts of industrial effluents from industries handling or producing cancer-related chemicals and of exhausts of motor vehicles have been released into the atmosphere. Between 1900 and 1948 there was an overall rise in the

production of these cancer-related industrial chemicals: bituminous coal, fuel briquets, carbon black, petroleum, asphalt (from petroleum), coal tar, isopropyl alcohol, asbestos, arsenic and chromite (cf. Figs. 1 and 2 infra). Data collected by others indicate pollution of the atmosphere of cities by 3,4-benzpyrene, the degree of pollution depending on weather and season. Of course 3,4-benzpyrene is but one of several carcinogenic hydrocarbons found during the incomplete combustion of carbonaceous fuel (coal, oil, gasoline). Under the traffic conditions prevailing in congested cities gasoline motors give off appreciable amounts of 3,4-benzpyrene, as do diesel engines under conditions of strain or improper adjustment. Hueper also lists the oxidized aliphatic hydrocarbons mentioned by Kotin as potential human carcinogens in view of their effect on experimental animals. In fact, he places this effect in sharp contrast with the less successful efforts with the cutaneous application and inhalation of tobacco and cigarette tar and smoke to mice and rabbits, as well as the equivocal identification of appreciable amounts of a chemical carcinogen in cigarette smoke. His observation that the presence of 3,4-benzpyrene in tobacco smoke is a controversial issue is dated now by virtue of the fact that it has been

V-A-9

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definitely identified in the smoke, albeit in minute quantities. As he says, it would be difficult to account for the claimed carcinogenic property of tobacco smoke on the basis of this or any other known ingredient, and even Wynder agrees (1299-A).

Hueper rejects arsenic, representing the insecticide residue on the tobacco, as the active carcinogen, on the ground that although "Turkish" tobaccos have a low arsenic content lung cancer rates have risen in countries where these tobaccos are predominantly smoked. One might add that Wynder has abandoned the charge that arsenic is responsible, and that arsenic is no longer generally used as an insecticide in the United States, having been abandoned a number of years ago. Nevertheless one of the properties of arsenic is its capacity to remain in the soil of a field on which it is applied and appear for several years in the leaves of crops grown on the field. Hueper does not deal with arsenious oxide as an atmospheric pollutant.

Of great interest is Hueper's point that carcinogenic compounds from motor vehicles are released at ground level, where they can act on humans before becoming diluted. He cites the observations of Fitton showing the varying amounts of carbon monoxide from

V-A-10

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cars at increasing heights, from which he concludes that the human exposure to the harmful contents of automobile exhausts must vary greatly in the urban resident and worker with the locality, the height above the street, the density of traffic, its speed, continuity, the weather and other factors.

8. In response to the attempt to minimize the importance of occupational exposure in lung cancer etiology, Hueper advances the analysis of Metropolitan Life Insurance Company death rates by Lew (672), who found markedly higher rates among white male industrial policyholders than those for white men in the general population. The reasons for these higher death rates must be sought, according to Lew, in some environmental and occupational factors which are also responsible for the geographical variations in death rates from respiratory cancer, which are high in most industrialized and urban states and low in most agricultural states.

9. Finally, Hueper buttresses his findings with the following factors inveighing against a causal role in cigarettes: cigarette tar is but a weak carcinogen to the skin of mice in the hands of most investigators; unlike coal tar, cigarette tar does not produce cancers of the human skin and lip and cigarette smoking has no consistently positive correlation

statistically with cancers of the tongue and oral cavity.

In one of the last papers by the late Dr. Kennaway, he and Lindsey (2822) set down some interesting thoughts on air pollution, which are entitled to attention in any overall treatment of the subject:

"Atmospheric pollution in relation to cancer of the lung has been the subject of a good deal of confused thinking, and recently has acquired a spurious importance from the desire to exculpate tobacco. The notes below represent an attempt to lessen this confusion and do not claim to establish any final conclusions.

By about 1840 the smoky atmosphere of the Industrial Revolution of the 18th and 19th centuries in England had produced a change in coloration to black in about 70 species of moths\* \* \*. The story of the moths is by no means a wholly academic one as it provides quite independent evidence on the subject of atmospheric pollution\* \* \*. Kettlewell's (data show): (i) a correlation between industrial areas and a high percentage of the black form of moth; (ii) absence of melanic moths from pollution-free areas\* \* \*; (iii) a high proportion of melanic moths to the east of all industrial areas extending as far as the whole of the east coast. This probably reflects indirect effects of the drift of pollution due to the prevailing south-westerly wind.

During the present century, certain factors tending to reduce atmospheric pollution have been active, namely, the more economical combustion of smoke-producing fuels, and the replacement of these fuels by coal-gas and electricity; this second factor is of especial importance in relation to domestic heating and cooking, as the coal-fired household grate and range are the chief sources of atmospheric smoke. There is no doubt that

remedial measures can be very effectual: for example, Pittsburgh (USA) has been transformed from one of the dirtiest cities in the world to one of the cleanest. These factors tending to reduce atmospheric smoke are the exact opposite of anything which could account for the sudden increase in cancer of the lung in Great Britain in the period 1920-25, which increase has continued until the present day.

Any estimate of the total intake by man of any constituent common to coal smoke and to cigarette smoke (e.g., arsenic, 3,4-benzpyrene), though we have now sufficient data to make such an estimate fairly accurate arithmetically, is misleading in relation to the etiology of cancer of the lung. Tobacco smoke reaches the respiratory tract solely through the mouth, whereas most of the air which we inspire passes through the very efficient nasal filter which arrests 80% of particles larger than 2.5 m.

This consideration is of great importance in relation to the following observations.

i. Experiments in which animals (e.g., mice, hamsters) are kept in atmospheres containing tobacco smoke are misleading in relation to cancer of the lung in man, because these animals do not keep their mouths open for the purpose of the experiment, and, in many rodents, the structure of the turbinate bones is much more complex than it is in man.

ii. The comparison of data from different countries, and even from different areas of the same country, is made difficult by the fact that atmospheric pollution is not of a uniform character. Thus one could select two towns, say, in Norway and England, where a given volume of air contains the same amount of suspended matter; but it may not be of the same composition and certainly may not contain the same amount of the same carcinogens, or of cocarcinogens. Our methods of estimation measure blackness, which is affected by substances which are not black - road dust for example. Thus the suspended matter of Los Angeles is said to contain large amounts of gasoline, while the corresponding material in Reykjavik is probably composed largely of road dust.

That the increase of cancer of the lung of recent years is of occupational or industrial origin (Hueper [970-B] was shown to be extremely improbable ten years ago [216] by the fact that the number of deaths in two large groups (coal-miners and agricultural workers) in which the incidence was, and is, very low, was increasing at the same rate as in the general population of England and Wales\* \* \*.

The various possibilities of carcinogenic and cocarcinogenic action in such materials as the suspended matter of the air of a town are considerable. Thus, in any one case there might be: a single carcinogen; more than one carcinogen, the effects of which might summate; one or more cocarcinogens; solvents of carcinogens [1559], particles with various powers of adsorbing carcinogens and cocarcinogens [118]; and all of these may vary with the time of the year and the locality."

Shimkin (3030) has written that the studies on the relationship between smoking and lung cancer have been so extensive and convincing since 1950 that there is no other conclusion but that smoking is one of the causes of this neoplasm. At the same time, however, he concedes that there is a need for additional studies of the urbanization and occupational factors in lung and other cancers, and for the control of atmospheric pollution from individual as well as industrial sources. In acknowledging that the assignment of a causal role to smoking does not mean that all problems and questions are solved, he says:

"The conclusion of a causal role of smoking in cancer of the lung does not imply that all problems and questions regarding the mechanism are solved. Indeed, it opens up some intriguing facets of epidemiology and experimental pathology, such as

I-A-14

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why the male-female ratios among Mexicans in the Los Angeles area are closer to unity than elsewhere [2147], or why the trachea is so immune to carcinogenesis by chromite and other carcinogenic materials as well as tobacco tars. Nor does it suggest that smoking is the only cause of lung cancer, since at least five other materials that gain access to the lung have been established as being carcinogenic: pitchblende, coal-gas, chromite, asbestos, and hematite, and there are probably dozens more in the field of environmental inhalants alone. Moreover, the conclusion of course does not indicate that research in cancer should now be directed only toward smoking; quite the reverse, the data have opened new approaches and should lead to accentuation upon a broad front of research."

Roegholt (1065-B) considered the two major alleged causes of lung cancer, namely, cigarette smoking and air pollution, and concluded that the increase of this disease is not caused by smoking. It is more probable in his opinion that the exhaust products of internal combustion engines are responsible for the recorded lung cancer increase. He plotted graphically the increase in the number of motor vehicles together with the increase in lung cancer mortality of men per 10,000 capita. Between these two curves so plotted he detects an analogy in form and a difference in years corresponding with the period of incubation of carcinoma in general. The cause of the increasing incidence of lung cancer is due to the introduction to our environment of an exogenous factor beginning about 1910 to 1920 and having an increasing influence thereafter. Of course the motor vehicle meets this description.

V-A-15

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Roegholt states that other factors also parallel the lung cancer curve but do not allow for a latency period by preceding the rise of the lung cancer curve.

For support of his thesis that exhaust products of engines are responsible for the great increase in lung cancer Roegholt cited the work of Kotin with atmospheric extracts from Los Angeles. Roegholt also referred to a study by Cooper with regard to air pollutants in large towns in England, which found soot with adsorbed hydrocarbons including 3,4-benzpyrene. Roegholt may have gone a little astray by stating that cigarette smoke does not contain any 3,4-benzpyrene itself. For this he apparently relied on Cooper, whose paper was published before those announcing the detection of that substance in cigarette smoke. Cooper also suggested that cigarette smoke might promote carcinogenic action by dissolving the 3,4-benzpyrene adsorbed on the particles of carbon retained in the lung. Cooper expressed the view, however, that atmospheric pollution by smoke cannot alone account for the increase in lung cancer, and referred to the exhaust gases of internal combustion engines and the high temperature combustion of other materials.

Roegholt announced that Utrecht University had recorded beginning in 1921 an increasing incidence of lung cancer in dogs (cf. Ten Thije and Ressang (1114) infra).

He quite properly notes that there is a much more likely explanation for this phenomenon in the exhaust products of motor vehicles than in smoking. He is inclined to accept 3,4-benzpyrene as the cause of lung cancer before internal combustion engines were invented in view of the fact that since it is a by-product of all combustion processes exposure to it has always been possible. As to the male-female disparity, Roegholt thinks men are more exposed to motor exhaust than women and that if smoking were the cause of lung cancer the fact that more women have become smokers should have narrowed the gap.

Eckardt (924) reviewed some of the work done in the field of environmental cancer and has pointed out some inconsistencies which to him demand that we proceed with caution in the adoption of measures to reduce air pollution or curtail the use of cigarettes. He comments that our knowledge of environmental cancer, with the exception of sporadic clinical observations similar to those made by Sir Percival Pott (334) in chimney sweeps really only dates from 1915 when Yamagiwa and Ichikawa (476, 477) succeeded in producing mouse skin cancer by applications of coal tar. Specific knowledge of occupational bladder cancer itself only dates from the work of Hueper in 1938. In view of the

V-A-17

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infancy of medicine's understanding of environmental cancer he advises caution in the interpretation of the vast multitude of literature on the subject. He asks whether the increasing number of automobiles means that we have increased the amount of 3,4-benzpyrene in the air (the presence of which in the atmosphere dates at least since 1775 when Pott identified chimney sweeps cancer). Data supplied from Salford, England, by Cooper (76, 77) suggests that the 3,4-benzpyrene content of the air in that city is from 8 to 9 times as great as the 3,4-benzpyrene content of the air over Los Angeles where there is said to be a very high concentration of automobiles. Eckardt concludes that coal would appear to be a much greater contributor to the 3,4-benzpyrene content of the air than automobiles. He cites Kreyberg's work in Norway as injecting doubt into the proposition that the concentration of industry in our cities is responsible. Kreyberg showed that lung cancer in Norway, although related to urbanization, is not related to industrialization. Finally, Eckardt questions how air pollution, if responsible, can account for the sex difference in the incidence of lung cancer.

Kotin (982) argues that atmospheric pollution plays a dominant part in a real increase in lung cancer occurring in various parts of the world. He points to

other agents, including excessive use of tobacco, as being capable of playing only a secondary role, possibly acting in conjunction with other factors as additives or as cocarcinogens. He reserves more definitive judgment until refinements in the epidemiologic and laboratory data are available.

In 1957, Macdonald flatly told the Blatnik Committee at hearings on filter-tip cigarette advertisement that the cause of lung cancer is much more complicated than the oversimplified thesis of cigarette smoke (2084). After attacking the evidence advanced by supporters of the tobacco theory, he turned to the subject of air pollution in urban areas, and voiced the opinion that to him the most reasonable explanation for the difference in the incidence of lung cancer in urban and rural areas was the sharp increases in production or consumption of cancer-related industrial chemicals and other concomitants of industrial growth. He referred to Hammond's published data showing an increase in mileage of state asphalt highways and national consumption of motor fuel--both of which he stated were considerably greater in relative increase than cigarettes. He pointed out also that fuel oil sales, and motor vehicle registrations paralleled the increase in

V-A-19

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lung cancer. Similarly, he reminded the Committee that there have been sharp increases in carbon black, petroleum, coal tar, asbestos, arsenic, and chromite.

As evidence of the importance of industrialization in the etiology of lung cancer, he stated:

"It has been estimated that 6 tons of tarry material fall on each square mile of Manhattan every year, and walking down Fifth Avenue or Madison Avenue can well convince one of that fact. In English towns, various studies have shown that the number of lung-cancer deaths increases in proportion to the number of chimneys per acre in the towns studied."

Before the Blatnik Committee, Greene also (2075-A) pointed out that many factors in man's environment have changed in the past 50 years, and that several of these relate directly to the lung. He enumerated the pollution of atmosphere with the exhaust gases of industry and automobiles, together with the more frequent x-ray examination for early detection of tuberculosis. He testified that in his opinion there were many other factors showing an increase in prevalence comparable to that thought to obtain in lung cancer. As to the universality of the tobacco smoking habit, he testified that he doubted that the statistical association with tobacco smoking can be interpreted as showing a cause and effect relationship, and expressed the opinion that experiments conducted in an effort to confirm the

J-A-20

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statistical approach have not succeeded in their purpose.

The National Conference on Air Pollution, held in Washington, D. C., November 18-20, 1958, under the auspices of the United States Public Health Service, brought out many experts on air pollution. The subjects discussed included the extent of air pollution, its sources, health effects of air pollution, economic and social effects, control methods and procedures and administrative aspects (3828).

Many authorities stated their opinions on air pollution. In subsequent sections, we have outlined some of the evidence on which these opinions are based.

Those authorities whose comments were of particular interest to the problems of the Tobacco Industry were: Leroy E. Burney, Leslie A. Chambers, Herbert McKee, James P. Dixon, William E. Scott, Arthur E. Stern, Morris B. Jacobs, Rolf Eliassen, William F. Ashe, Lester Breslow, Norton Nelson, John R. Goldsmith, Reginald H. Smart, Thomas F. Mancuso, Paul Kotin, Dean F. Davies, Geoffrey C. Carey and James L. Whittenberger.

Indicative of the state of confusion existing with regard to the theory of lung cancer causation, opinions vary as follows:

1. Air pollution is one of the most important

V-A-21

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- factors in lung cancer causation.
2. Air pollution and cigarette smoke are both important factors in lung cancer causation. The extent of participation of each of these factors is unknown.
  3. Cigarette smoke is one of the most important factors in lung cancer causation.
  4. Neither air pollution nor cigarette smoke is an important factor in lung causation.
  5. Multiple factors, e.g., air pollution, cigarette smoke, inherent susceptibility, hormone balance, socio-economic factors, etc., are responsible for lung cancer causation.

There follows a collection of comments from writers illustrating these various points of view. In most cases the publication was in the nature of a review of work done in the field and an expression of opinion on that work without the contribution of original research by the author.

Andrews (805) considers air pollution as one of the most important factors in lung cancer causation and stresses the importance of preventive measures.

V-A-22

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Dontenwill (1145) argues that lung cancer in Iceland is on the increase not because of the increased cigarette consumption by the population but because of the increase in air pollutants. He pointed out that the number of miles of asphalt roads has increased much more than the consumption of cigarettes during the past several decades.

Firket (934-A) in an interesting study of the city of Liege plotted the areas with increasing industrialization on one map and the areas with increased lung cancer incidence on another. The two maps were almost superimposable. He pointed out that the air pollution in Liege has increased 10-fold during the period 1899-1931.

In another study, Firket (2771) noted:

"Of several causes [of lung cancer], cigarette smoking is very important, but not always an essential one. Indeed it seems that polluted air and particularly the hydrocarbons contained in soot remain the most important cause."

Clinical data collected by Firket indicated more lung cancer in industrial areas than in urban areas or in industrial areas swept clean by prevailing winds.

Vorwald (2911) suggested that the epidemiological, chemical, and biological data from air pollutant studies indicated that inhaled atmospheric pollutants were an important factor in lung cancer causation.

L'Eltore (991), in Italy, cited air pollution as

a major factor in lung cancer incidence, listing cigarette smoke as a minor factor only.

Bauer (872) suggested that coal tar products in air pollutants are responsible to a great extent for the incidence of lung cancer but he also noted that there probably was no single cause of this disease. He mentioned the parallelism between air pollution and lung cancer and between cigarette consumption and lung cancer.

Meyer et al. (1020) said that since laryngeal cancer was not increasing in frequency at the same rate as lung cancer, cigarette smoking was probably not an important factor with respect to lung cancer. They considered air pollution important but also stressed the effect of increased use of antibiotics in recent years.

Hadidian (2531-C) wrote that the cause of lung cancer has not yet been adequately defined and thus, in the case of air pollutants, cigarette smoke, etc., there were no reasons to

"Abandon\* \* \*efforts to establish or deny conclusively a specific cause-and-effect relationship between these [inhalants] and pulmonary cancer."

Mider (1256) stressed the similarities in the evidence purporting to indict air pollutants or cigarette smoke as causal agents for lung cancer.

Waller (2912) deprecated the importance attached

) to air pollutants as a cause of cancer of the lung.

Joules (662, 1237), Higgins (2540), and O'Donnell (2607), plus the authors of most of the retrospective and prospective studies which are treated as proof of an association between cigarette smoking and lung cancer, are of the opinion that the evidence available to date indicates that cigarette smoke is a more important factor in lung cancer causation than air pollutants.

Korteweg (668-A) pointed out that there was a possibility of cooperation between the weak carcinogenicity of cigarette smoke and the weak carcinogens in air pollutants in lung cancer causation. These two factors, according to him, are the only ones worthy of consideration.

Schweisheimer (2883) claimed that neither air pollution nor cigarette smoke is an important factor in lung cancer causation.



## 2. EPIDEMIOLOGICAL STUDIES

### a. Human

A greater incidence of lung cancer has been observed in urban residents than in rural residents. Those statistical studies of the alleged association between cigarette smoking and cancer which also considered residence found such an urban excess.

Other studies, measuring residence and lung cancer mortality against vital statistics without employing a specific control population, have also demonstrated an excess of lung cancer mortality among urban residents. There have been relatively few of the latter type of study, but they have almost uniformly disclosed an urban excess. The following will briefly discuss such studies in the belief that they are peculiar to the subject of this section and hence warrant inclusion here.

Employing vital statistics collected in the United States for the years 1948 and 1949, Hoffman and Gilliam (654-A) showed that in all age, race, and sex components the rate for lung cancer was greater for urban than for rural residents. See Table X herein, substantially reproduced from their paper. The definition of urban residents employed by Hoffman and Gilliam was that of the 1940 census, i.e., comprising those persons living in places of 2,500 or more persons.

They claimed that their data, and similar data from other countries are not sufficient in themselves to determine the occupational, environmental, economic, diagnostic, etc., factors responsible for the differences. Another study of vital statistics demonstrating an excess mortality from lung cancer in urban residents is that of Herbach et al. (654). Their findings were summarized in a table, which is reproduced here as Table XI. Unlike Hoffman and Gilliam, who divided the United States into only two groups, Herbach and his co-workers dealt with four groups in Austria. Their study was limited to males; Hoffman and Gilliam's figures are for both sexes. A progressively increasing lung cancer mortality was found by Herbach et al., with the lowest rate in the rural group, except that the rate in the smaller cities was slightly more than that in the larger cities other than Vienna.

Clemmesen et al. (70) studied the incidence and mortality of lung cancer in Denmark using data collected by the Central Tuberculosis Station for Denmark, and found a higher mortality rate for lung cancer in urban areas than in rural areas. From 1931 to 1950 the approximate mortality per 100,000 males for these areas changed as follows:

<u>Areas</u>	<u>1931</u>	<u>1950</u>
Copenhagen	5	40
Provincial Towns	2	12
Rural Areas	2	8

TABLE X

URBAN AND RURAL POPULATION (1950) AND DEATHS FROM LUNG CANCER (1948-1949) IN THE  
UNITED STATES, ACCORDING TO AGE AND SEX [ADAPTED FROM (654-A)]

Race and Sex	Urban			Rural			United States Totals		
	Pop'n (millions)	Deaths		Pop'n (millions)	Deaths		Pop'n (millions)	Deaths	
		Actual	Per 100,000		Actual	Per 100,000		Actual	Per 100,000
<u>White</u>									
male	38.70	18,201	47.0	28.42	6,711	23.6	67.12	24,912	37.1
female	40.97	4,358	10.6	26.84	1,888	7.0	67.81	6,246	9.2
<u>Nonwhite</u>									
male	4.42	1,244	28.1	3.28	354	10.8	7.70	1,598	20.8
female	4.84	326	6.7	3.21	98	3.1	8.05	424	5.2
TOTAL	88.93	24,129	27.1	61.76	9,051	14.6	150.68	33,180	22.0

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TABLE XILUNG CANCER MORTALITY RATES PER 1,000  
DEATHS, MALES IN AUSTRIA, 1954 (654)Community

Vienna	59.0
Cities 60,000-1,000,000	31.6
Cities 20,000-60,000	32.3
Remainder of Austria	17.3

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The above data were interpolated from a graph included by the authors in their paper, and hence are approximations.

In a comparable study using data collected by the Danish Cancer Registry for Denmark for the years 1942-1952, Clemmesen, et al., (1552-C) found, as they had in their earlier study, a higher incidence of lung cancer in urban areas. Both in this study and in the earlier study, however, they refused to ascribe the result to atmospheric pollution except for small areas. They reason as follows in the later study:

"For small areas atmospheric pollution may perhaps be a local factor of some importance, but the assumption that it plays a part in the genesis of lung cancer is not necessary to explain the differences in incidence of this disease between urban and rural areas, which probably are expressions of a difference in the time for the beginning of the exposure to the carcinogen."

The results, they argue, are equally well explained by the supposition that the carcinogenic influences responsible began a few years later in the provincial towns than in Copenhagen and still later in the rural areas. In a third paper, they attribute the differences to smoking habits. It seems clear, however, that the results are also on their face some evidence of the guilt of atmospheric pollution. The fact that there was an increase in all three areas studied between 1931 and 1950 would appear offhand to be a manifestation of increasing industrialization of all three areas and perhaps increased

TABLE XII

LUNG CANCER DEATH RATES IN 25 STATES OF THE UNITED STATES,  
1946 AND 1948, CRUDE DEATH RATES PER 100,000

<u>State</u>	<u>1946</u>	<u>1948</u>
<b>Industrialized States</b>		
Connecticut	8.5	11.1
Illinois	8.1	8.2
Maryland	6.5	8.4
Massachusetts	10.4	10.2
Michigan	5.7	7.1
New Hampshire	7.4	10.1
New Jersey	9.7	9.7
New York	10.2	11.9
Ohio	6.0	7.3
Pennsylvania	6.7	8.4
Rhode Island	8.7	7.4
<b>States with Regional Industrialization</b>		
Florida	6.8	7.4
Louisiana	6.5	8.5
Missouri	7.3	9.4
Montana	10.0	8.8
Nebraska	5.7	8.0
<b>Agricultural States</b>		
Alabama	4.0	5.1
Arkansas	3.6	5.4
New Mexico	2.6	3.0
North Carolina	3.1	4.0
North Dakota	5.6	4.1
Oregon	4.1	4.4
South Carolina	3.6	3.7
Washington	5.1	4.2
Wyoming	4.9	3.9

The death rates for the year 1946 were taken from "The American Cancer Society, Inc., 1949, Cancer Death Rates for each State in the United States by Site," those for the year 1948 were produced by the National Office of Vital Statistics.

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pollution of rural areas by proximity to the undoubtedly expanded industrial facilities of towns.

Clemmesen et al. also reviewed the work of others in some 11 other countries, stating that the figures for all of the other countries except Great Britain confirmed their conclusion that the recorded association in each case between urban incidence and lung cancer was not sufficient to postulate atmospheric pollution as an etiologic factor. As to Great Britain, they reluctantly conceded that an association was shown in view of the much more intense urbanization there than in essentially rural Denmark and the relatively more rural other countries considered.

Hueper (970-B) interprets the urban excess mortality quite differently from Clemmesen et al. in that he considers that atmospheric pollution is the predominant cause of lung cancer. His paper shows higher age-adjusted death rates from lung cancer for white males in the United States for 1946 and 1948 for those states with higher degrees of urbanization. See Table XII, which has been taken from Hueper's paper.

The gradation of lung cancer incidence in males according to degree of urbanization is emphasized in the results of a study conducted by Stocks (415) in towns and cities of England of varying sizes. The

progressive increase in mortality accompanying population concentration is shown in Table XIII also taken from his published report. That table shows the comparative mortality ratios for males in the various areas studied for the period 1946-1949 as a function of deviations from the average lung cancer mortality rate arbitrarily assigned a value of 100.

For several years Hammond (650-D) felt that atmospheric pollution was one of the major causes of lung cancer. However, he stated in 1954 that if the prospective statistical studies then in progress on the relationship between lung cancer and cigarette smoking confirmed the findings of the numerous retrospective studies, he would accept cigarette smoke as the more likely cause. Before publication of the results of the prospective studies he listed asphalt highways, coal, motor fuel, fuel oil and automobile exhausts (as measured by motor vehicle registration) in addition to cigarette smoke as likely etiologic factors in lung cancer causation. He cited some of the laboratory evidence, based on chemical and biological studies, tending to incriminate each of the factors listed, and also plotted a graph showing the time-quantity relationship involved with these commodities. The significance of this graph, which is reproduced herein as Figure 1, lies in the apparent parallel

V-A-30

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TABLE XIII

COMPARATIVE MORTALITY RATIOS FROM LUNG CANCER  
FOR MALES IN 1946-1949 (415)

Groups of adjacent towns with over 200,000 occupied dwellings	
London, East Ham, West Ham, Croydon	156
Birmingham, Smethwilk, Walsall, W. Bromwich	134
Manchester, Salford, Stockport	159
Liverpool, Bootle, Birkenhead, Wallasey	162
Leeds, Bradford, Halifax	132
Sheffield (124,000 occupied dwellings)	135
Newcastle and Gateshead (87,000 occupied dwellings)	114
Aggregate of 6 towns, each with 50,000 to 85,000 occupied dwellings	113
Aggregate of 3 towns, each with 40,000 to 50,000 occupied dwellings	107
Aggregate of 12 towns, each with 30,000 to 40,000 occupied dwellings	104
Aggregate of 13 towns, each with 20,000 to 30,000 occupied dwellings	100
Aggregate of 29 towns, each with less than 20,000 occupied dwellings	89

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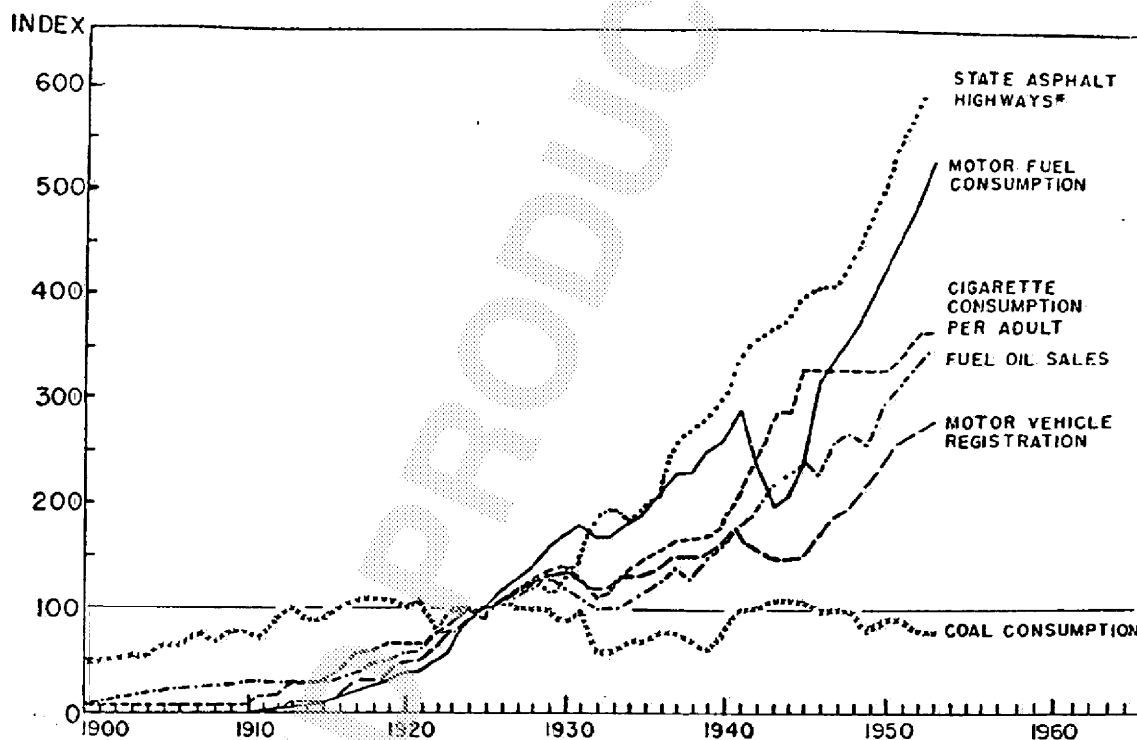
between the increased consumption of these commodities and the alleged increase in lung cancer. It may be noted from Figure 1 that coal consumption in the United States has remained at an almost constant level for the past 50 years, whereas the other commodities plotted have increased by factors of about 3 to 12 during the same period.

Similar data on the time-quantity relationships involved with many suspected cancer-causing factors in man's environment have of course been published or referred to by others. See, for example, Roegholt (1065-B) and Hueper (970-B) in the introduction to Environmental Factors. Figure 2 is reproduced from Hueper (970-B).

With the publication of the results of his and other prospective statistical studies inquiring into the association between smoking and cancer, Hammond announced (153) that not only was an association between cigarette smoke and lung cancer demonstrated but the relationship was one of cause and effect.

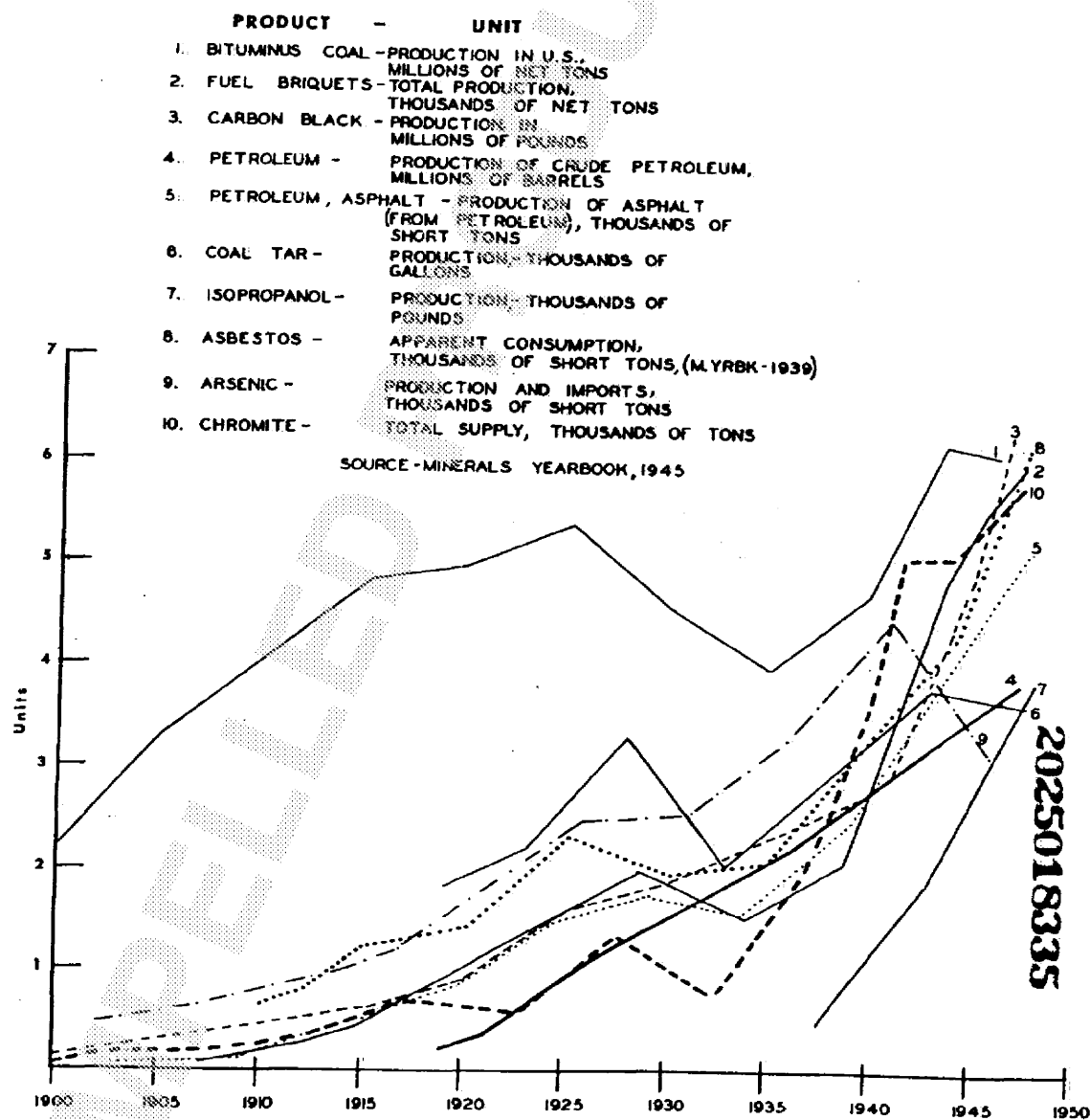
In a retrospective statistical study of the relationship between tobacco smoking, motor exhaust fumes and lung cancer incidence, Mills and Mills-Porter (2333) contended that tobacco smoking was found to be significantly related to lung cancer incidence "whether or not there was in addition heavy exposure in urban

Figure 1. Trends in selected environmental factors, United States, 1900-53 (Hammond).



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Figure 2. Rise in annual production or consumption of cancer-related industrial chemicals between 1900 and 1948.



motor traffic or to general urban air pollution". But they found that annual driving mileages above 12,000 miles per year, as compared with lesser driving mileages, were significantly related to lung cancer incidence, except for those in the heavy smoking category. In addition, their findings showed that lung cancer death frequencies were significantly higher among Cincinnati Basin men than among suburban men in their survey.

In a study of the environmental histories of persons with and without cancer, Stocks and Campbell (1104-A) calculated the death rates from lung cancer among men of different smoking habits living in rural areas in Wales, in a mixed area, and in an urban area, Liverpool. The death rates were then related to the quantity of 3,4-benzpyrene in the air at various places within those areas. The authors reported the following:

"The absolute urban excess is much the same in each smoking group, suggesting that an 'urban' factor is added to the effects of smoking. Differences in smoking habits of the population can account for only a small fraction of the contrasts of total rates, and it is estimated that about half the Liverpool deaths from lung cancer arise from cigarette smoking and about three-quarters of the remaining half are due to a factor which is only slightly present in the rural area."

Note the high content of speculation inherent in the

foregoing appraisal of the degree of responsibility of the possible etiologic factors mentioned.

When various pollutants of the atmosphere were considered, and in particular 3,4-benzpyrene, the authors rationalized as follows:

"The concentration of smoke and of 3,4-benzpyrene, other polycyclic hydrocarbons, and sulfur dioxide in the air rises with increasing urbanization, the benzpyrene figure in Liverpool being 8 to 11 times as great as in the rural localities examined, a ratio which corresponds with the estimated mortality ratio amongst non-smokers living in those areas. When the death rates are compared with the calculated total intake, by different categories of smokers in the areas, of benzpyrene derived from air according to certain assumptions, plus that derived from the number of cigarettes smoked, the degree of correspondence is such as to suggest that benzpyrene might be the one agent involved."

With respect to the latter suggestion, Wynder has categorically denied, even as recently as February 1959, that the amount of 3,4-benzpyrene in cigarette smoke is great enough to elicit the number of tumors observed in his experimental animals (3525), e.g.:

". . . it is generally realized, of course, that this amount of benzpyrene [2 micrograms per 100 cigarettes] is not sufficient to account by itself for the carcinogenic activity of the total tar. . ."

In a more recent paper, Stocks (3804) studied the relationship between lung cancer and bronchitis mortality and exposure to atmospheric deposit and smoke in Lancashire and the West Riding of Yorkshire. Bronchitis

showed a significant correlation with atmospheric deposit but not with smoke; lung cancer showed the reverse relationship. Stocks concluded:

"In Lancashire areas, lung cancer is strongly correlated with population density in adjacent districts even when that of the areas itself is held constant, and this appears to confirm the effect of wind-borne smoke on the incidence of the disease."

The author assumed that the "smoke" behaved in the same way as sulfur dioxide, the presence of which is readily detected in the atmosphere. This might also imply that the compounds described by Kotin et al. (3474), e.g., the oxidized aliphatic derivatives from gasoline, would behave similarly.

The only study of which we are aware that has not observed an urban excess is one by Lickint (1383). He found that respiratory cancer constituted 17.3 percent of all cancers in the rural area of Schleswig-Holstein but only 8.2 percent of all cancers in the highly industrialized area of Nordrhein-Westfalen.

Haenszel (954) has pointed out, and probably correctly too, that very few controlled epidemiological studies of the relationship between air pollution and lung cancer have been conducted. He comments:

"Those advancing atmospheric carcinogen theories have pointed to the sizeable urban-rural differentials in lung cancer risks [1706-E], although some further assumptions are required to reconcile

this hypothesis with the great excess risk observed among males. The presence of carcinogenic substances in urban atmospheres has been repeatedly demonstrated by experiments with mice [237-A, 257]. Further epidemiological work has been hampered by the inability to classify individuals in the general population quantitatively with respect to atmospheric exposures . . . ."

By contrast with studies concerning atmospheric pollution, epidemiological studies relating lung cancer and smoking have been relatively simple to define. Disregarding a host of factors, in most cases the investigators limited themselves to a few questions pertaining to smoking habits, e.g., "Do you smoke? If so, what and how much?" in the case of the prospective statistical studies; or "Did the deceased smoke? If so, what and how much?" in the case of the retrospective studies where the questions were asked of the deceased's relatives, friends, etc. Examination of the questionnaires employed in a large percentage of these studies relating smoking and lung cancer will verify this point.

The epidemiological studies relating atmospheric pollution and lung cancer are rendered more difficult than those concerning smoking and lung cancer since so many factors are involved, e.g., automobile exhausts, factory and resident effluents, dust from asphalt roads and automobile tires, etc. A questionnaire designed to cover all such factors would be rather involved, to say the least. The epidemiologists concerned

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primarily with air pollution as a lung cancer cause are aware of the difficulties involved in their studies whereas their counterparts concerned primarily with tobacco smoking, for the most part ignore the fact that a factor other than tobacco smoke might be involved. An exception to this are the studies described by Mills and Mills-Porter (2333) in which the questionnaire dealt both with smoking and the number of miles driven in a motor vehicle.

Very few air pollution epidemiologists have stated categorically that Factor X or Factor Y, etc., is the major cause of lung cancer, whereas, for a time, some of the epidemiologists concerned with smoking did advance the claim that smoking was the major cause of lung cancer. Fortunately, this latter, rather biased viewpoint has almost disappeared during the past two years. Even the most vigorous proponents of the lung cancer-smoking theory have moderated their views, as shown by the following statements of Cornfield et al. (3409) published early in 1959:

"\* \* \* We can agree with Cohart, '\* \* \* that important environmental factors other than cigarette smoking exist that contribute to the causation of lung cancer'. These and other findings are convincing evidence for multiple causes of lung cancer. It is obviously untenable to regard smoking of tobacco as the sole cause of lung cancer."

b. Other Species

The increase in lung cancer incidence in humans residing in industrial areas has an interesting analogy in a recent study of specimens from the Philadelphia Zoological Gardens conducted by Lombard and Witte (3486-A). In 1935, the nutrition of the animals of this zoo was greatly improved. Comparison of the frequency of all malignant tumors for the period 1901-1934 with that for the period 1935-1955 showed an increase in frequency in 3 orders (primates, carnivora, artiodactyla) comprising 9 families of mammals and a decrease in 2 orders (rodentia, marsupalia).

With respect to benign tumors, only the order rodentia showed a decreased frequency between these two periods. The other 4 orders registered an increase in benign tumors.

The four orders of birds maintained at this zoo also showed an increased frequency between the two periods with respect to both malignant and benign tumors.

With respect to lung carcinoma it was observed that this tumor occurred predominantly in the later period. The high frequency of lung cancer in the order Anseriformes (goose) during the period 1945-1955 emphasized the importance of air pollution since

these birds were kept in outdoor pens throughout the year. Since completion of the survey involving the period 1901-1955, 5 additional lung carcinomas have been observed in this order.

The authors considered that both nutrition and environment may be considered as factors influencing the tumor frequency.

The results of another study on domestic animals, the dogs, were presented by Ten Thijs and Rensang (1914). From 1924 to 1954, they examined 9,781 dogs post-mortem and found that 22 had lung cancer. Sixteen of these cases were noted from 1951 to 1954. The tumors observed in every instance were quite large hence the more recent increase in this tumor could not be due to better examination. The tumor differed from the human type in that it was a cylindrical cell carcinoma. Krahnert (1983) also noted an increase in incidence of lung cancer in dogs.

However, a study of mice in Glasgow, Scotland by Peacock and Pullinger gave no evidence to support the idea that atmospheric pollution is a factor in the production of lung cancer. The lungs of old mice living in the animal house of the Royal Beatson Memorial Hospital regularly showed black pigmented spots at autopsy. Primary tumors of the lung in these

mice often were surrounded by a black halo suggesting the possible etiological importance of the great amount of soot in the atmosphere. To test this possible influence, one group of mice lived in an almost completely soot-free room while another group was exposed to the unfiltered air of central Glasgow. Although the study is not yet complete, it was obvious that there was no evidence to support the idea that atmospheric pollution is a major factor in the etiology of adenocarcinoma of the lung in C3Hf mice. Animals with no detectable soot in their lungs developed tumors as frequently as those whose lungs had obvious soot deposits (see Brit. Emp. Cancer Camp., Ann. Rept., 1958, 406).

Another negative report comes from California where Catcott (3087) examined 51 dogs at necropsy within 24 hours after death. The dogs were selected from two areas of Los Angeles County with contrasting patterns of air pollution. However, no pathological or morphological differences were observed in the tracheo-bronchial tract of the two groups.

V-A-39

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### 3. BIOLOGICAL STUDIES

Even though several types of cancer suspected, on the basis of clinical observations, to be caused by carcinogenic agents of an environmental nature had been described, e.g., "chimney sweep cancer" due to soot recorded by Pott in 1775 (334), "paraffin" cancer due to shale oil recorded by Bell in 1876 (27), "chimney sweep cancer" due to coal tar pitch described by Ross and Cropper (373) in 1913 and by Norris (306) in 1914, it was not until 1915 that tumors were produced in experimental animals by painting with coal tar solutions. In that year, two Japanese workers, Yamagiwa and Ichikawa (476, 477), announced the results of repeated applications of solutions of coal tar to rabbits' ears for a period of two years. Malignant tumors appeared at the site of application of the coal tar solution. These investigators described in careful detail the host of cellular changes observed during the tumor production, i.e., epithelial hyperplasia, keratinization, atypical proliferation, invasion, etc. This was the first time this gamut of cellular changes had been observed by man in experimental animals, and no investigator since has observed any other or dif-

V-A-40

2025018344

ferent cellular changes. The section on Pathogenesis will discuss other studies on cellular changes.

In 1918, the results of Yamagiwa and Ichikawa were confirmed by Tsutsui (438), who also noted that skin painting experiments using mice resulted in lung tumors by metastasis in addition to the skin tumors at site of application. The procedures developed by Tsutsui for skin painting experiments are employed almost without change today.

Since 1918, numerous other investigators have studied the carcinogenic activity of various industrial and occupational factors with the result that the number of factors found to be carcinogenic for one or more strains or species of animals is legion. The following is a list of some of these factors:

1. Coal tar by Bloch and Dreifuss (43), Deelman (95), Jorstad (211), Reding (340), de Coulon (83), Findlay (122), Bonne et al. (48-A), Tani (432), Cirio (68), McIntosh et al. (276), Murphy and Sturm (531) and Poel et al. (592).

It is of interest to note that Findlay (122) produced skin tumors by a single application of coal tar; that Cirio (68) found coal tar active in mice but inactive in guinea pigs; and that Bonne et al. (48-A) found coal tar to be non-

carcinogenic in monkeys even after prolonged and repeated treatment for a period of some 7-1/2 years. Coal tar, incidentally, is a common by-product of coke production and domestic and industrial heating employing coal.

2. Industrial tars by Hofmann et al. (180), Reding, (340), de Coulon (85), Taylor et al. (1113) and Shubik et al. (1189). Industrial tars are a high boiling by-product of the commercial cracking of coal tar and petroleum. In many of these experiments, the precise nature of the industrial tar was not clearly defined.
3. Soot by Twort and Twort (446), Campbell (60), Beck (873-A, 873-C) and Seelig and Benignus (1424).
4. Shale oil by Legge (253), Kennaway (214), Twort and Twort (445), Bogovski (48) and Sinai (1094).
5. Atmospheric dust (dust from the atmosphere of a subway) by Leiter et al. (256, 257), Kotin et al. (237-A) and Clemo et al. (70-A, 902-A).
6. Road dust and tar by Campbell (58, 60), Hogouneng (184) and Kling et al. (236).

7. Exhaust gases from automobile engines by Kotin et al. (237-B), from diesel engines by Falk et al. (572, 669) and "synthetic" exhaust gases by Falk et al. (931, 982-D, 982-E). "Synthetic" exhaust gases are those produced by a motor mounted in the laboratory or by treatment of gasoline with ozone. (see discussion of Kotin's studies, infra)
8. Gas works tar by Jordan (210).
9. Coal gas by Kuroda et al. (243).
10. Wood tar by Valade (537) and Dickens et al. (97-A).
11. Industrial rubber, e. g., automobile tires, by Falk et al. (119) and the carbon blacks contained in rubber goods and related products by Falk et al. (118) and von Hamm et al. (150).
12. Paraffin by Legge (253), Hofmann et al. ( 180) and Wood (470). It may be noted here that tobacco smoke contains paraffin hydrocarbons similar to those found in commercial paraffin. However, Wynder et al. have demonstrated that this paraffin fraction is noncarcinogenic (2054-E) to mice.



13. Lubricating oil by Legge (253) and Twort et al. (445); mineral oil by Twort et al. (446, 448); anthracene oil by Lacassagne et al. (246); and petroleum by Roffo (366), Hieger et al. (176) and Smith (1096).
14. "Isopropyl oil" by Weil et al. (462).  
"Isopropyl oil" is a by-product of the manufacture of isopropyl alcohol from propylene and presumably is a propylene polymer. Weil's study showed that six of 71 workers (8.4%) employed for more than five years in a plant manufacturing isopropyl alcohol who were exposed to the manufacturing process contracted cancer of the nasal sinus; in contrast, such cancers represent only 0.2% of all human cancers. (Martin, H., J.A.M.A., 137, 1366-1376 (1948)). Most commercial grades of isopropyl alcohol, a commonly used industrial solvent and an ingredient of many rubbing alcohols, yield measurable residues on evaporation. These residues conceivably could contain the "isopropyl oil".
15. Chromium and chromates by Hueper (1158-A) and asbestos by Nordmann et al. (1400).

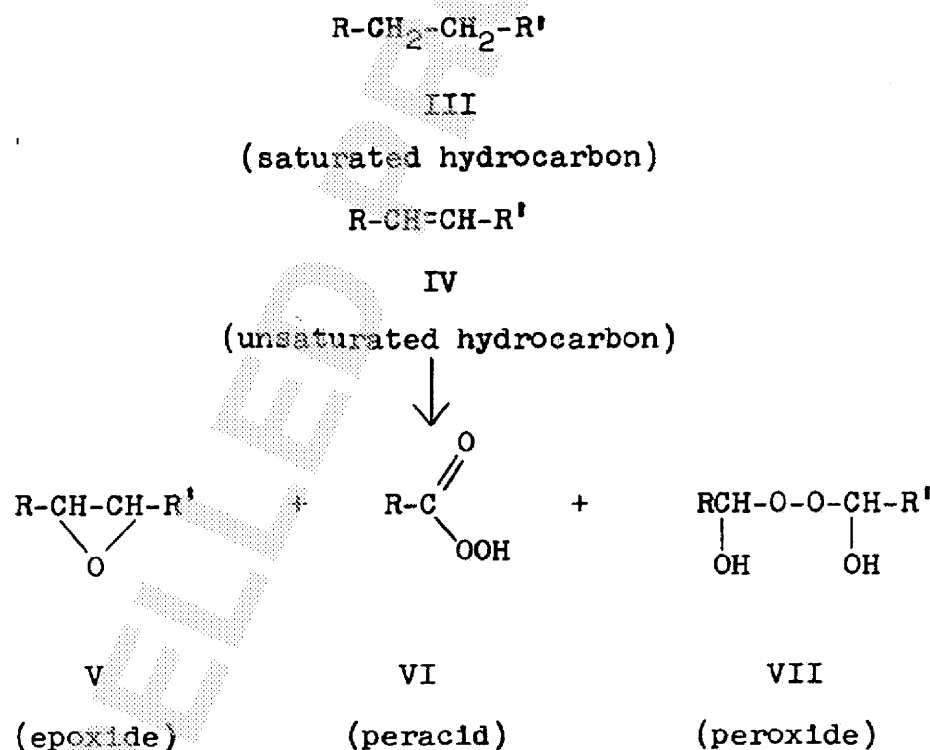
V-A-44

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It has been shown that all of the materials described in items 1 to 13 above contain one or more of the carcinogenic aromatic polycyclic hydrocarbons, with 3,4-benzpyrene being the most prevalent.

The presence of 3,4-benzpyrene or other polycyclic hydrocarbons is not a requisite for carcinogenic activity of certain atmospheric pollutants. Kotin et al. (3474) describe the results of experiments in which extracts of the exhaust products of gasoline engines, diesel engines, and the atmosphere were painted on the skin, or injected subcutaneously (under the skin), in C57BL and strain A mice. An unexpected finding, later confirmed in a duplicate experiment (982-D), was the production of tumors after painting and injection with the so-called control fraction, believed to be a noncarcinogenic fraction of the aerosol phase of the atmosphere, and known to be definitely free from carcinogenic aromatic polycyclic hydrocarbons (669-A). The number of tumors produced in the mice injected or painted with atmospheric and vehicular exhaust extracts was greater than could be accounted for by the 3,4-benzpyrene alone. (Cf. Wynder's remarks to the same effect on the carcinogenic activity of cigarette smoke and its 3,4-benzpyrene content (3525)).

The responsible agent in the so-called control fraction was thought by Kotin to be oxidized aliphatic hydrocarbons of the motor fuel used. Gasoline consists of about 80-85% of saturated hydrocarbons (III) and 15-20% of unsaturated hydrocarbons (IV). During the combustion process, the unsaturated hydrocarbons (IV) react with oxygen (oxidation) and yield certain oxidation products (V, VI, VII) which Kotin suspects to be carcinogenic.



V-A-46

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One may ask the question as to whether or not the above-cited animal experiments yielding positive results have any significance in terms of the human experience. Table XIV shows that the carcinogenic effect of these materials in animals has a clinically observed counterpart in humans, thus suggesting a plausible foundation on which the opposition may argue that extrapolation from animals to humans may be appropriate. Responsible scientists however have advised caution in drawing conclusions for humans on the basis of animal experiments (see discussion of Kotin below).

V-A-47

2025018351

TABLE XIVANIMAL VS. HUMAN EXPERIENCE

<u>Material</u>	<u>Effect in Human</u>	<u>Effect in Animal</u>
Anthracene oil	skin tumors, bladder tumors, scrotal tumors	skin tumors (246)
Creosote oil	skin tumors	skin tumors (379)
Petroleum products	skin tumors	skin tumors (18, 98, 110, 445)
Shale oil ) Lignite oil )	scrotal tumors vulvar tumors	skin tumors
Coal tar ) Pitch ) Asphalt )	skin tumors scrotal tumors	skin tumors, metastatic lung tumors
"Isopropyl oil"	nasal sinus tumors	lung tumors (462)
Estrogens (sex hormones)	mammary tumors (?)	tumors
Aromatic amines (dye intermediates)	bladder tumors	bladder tumors (204)
Benzol, a commercial solvent	leukemia	?
Chlorinated hydrocarbons (refrigerants, commercial solvents)	cirrhosis of liver	hepatomas (liver tumor)

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The proponents of the lung cancer-smoking theory point out that the evidence obtained by the above investigators for the various factors cited has been duplicated in skin painting experiments using tobacco smoke condensate by such workers as Wynder, et al., in various strains of mice (475, 599, 800-B, 1134, 1450, 1450-A, 2054-E, 2074, 2446-A, 2447, 2447-A, 2494, 3253) and in the rabbit (2231, 1354); Suguira (1289); Blacklock using the rat (2124); Neukomm (1849); and others. Wynder's study, the first of the foregoing, was published in 1953. The tars used in these experiments were obtained under conditions that the experimenters thought simulated the human smoking process. This involved the use of smoking machines of various kinds, and prompts the question whether such machines can ever truly duplicate the human smoking process. Other investigators, e.g., Passey (1046-B, 2864), Campbell (59) and Hamer, et al. (955, 955-A), could not duplicate Wynder's results with cigarette smoke condensate obtained in similar fashion and applied in lesser amounts. It is important to note in answering the tobacco smoke theorists that the amounts of cigarette smoke condensate applied to the test animals in the experiments yielding positive results were far in excess of the

2025018353

tars, etc., applied in experiments studying the other aforementioned environmental materials.

Many of the tumors in animals produced by skin painting with materials other than tobacco smoke condensate have been papillomas, which are benign. It has been demonstrated recently, however, that the tumors produced in mice by cigarette smoke condensates are indeed true cancers. This has been done by transplantation experiments, which are significant in that benign tumors cannot be transplanted from one animal to another, whereas one of the characteristics of malignant tumors is their ability to be transplanted. The results of a study conducted by Croninger, et al. (3537-A), show that tumors produced by skin painting with tobacco smoke condensate were successfully transplanted 102 times and yielded metastases to the lung and lymph nodes in 81 percent of the transplants.

As noted in a preceding section, there have been many earlier reports on the carcinogenic activity of tobacco tar but these results were obtained using destructive distillates from tobacco, e.g., Roffo from 1930 to 1945 (345, 346, 346-A, 349, 350, etc.), Flory in 1941 (127), and others. Wynder et al. (475) discounted these earlier ex-

2025018354

periments because the tobacco tar was not obtained under conditions simulating the human smoking process.

Lung tumors have been successfully produced in mice by a variety of methods and materials. The early literature is well reviewed by Magnus (280). The following discussion is taken from that review. The literature on the experimental production of lung tumors by carcinogens can be considered under two headings, those produced by the direct introduction of carcinogens into the lung and those produced by the application or introduction of carcinogens at a remote part of the body (indirect). The direct introduction method has seen the greatest success with the use of dust containing various tar derivatives.

In 1923 Kimura introduced crude coal tar into the lungs of anesthetized animals through a tracheotomy opening. One rabbit and 3 guinea pigs survived the operation; the rabbit developed a small adenomatous area and 1 guinea pig developed an adenocarcinoma (glandular cancer).

In 1928 Willis and Brutsaert produced tumor-like structures in the lungs of 7 out of 87 guinea pigs subjected to very long inhalation of an



atmosphere rich in silicon carbide dust. In the same year Smith found no tumors by exposure of mice for periods up to 409 hours to gasoline exhaust fumes and to coal tar fumes. In 1931 areas of hyperplasia were produced by Garschin and Pigalew in the lungs of rabbits by intropulmonary injection of tar into the lungs of rabbits, but no true tumors resulted. Coal tar introduced into the lungs of guinea pigs by a syringe inserted into the trachea also produced negative results for Schabad.

In 1934, Campbell (59) obtained up to 80% lung tumors among experimental mice exposed to dust from tarred roads while only 8% among the controls. He repeated the experiment with exhaust gases and cigarette smoke but produced only an insignificant increase in lung tumors. In 1936 Seelig et al., using a tumor-resistant strain of mice, showed an increase in adenocarcinomata and hyperplasia when forced to live on a bedding of coal smoke soot for a period of 18 months.

Andervont (3-A) in 1937 produced adenomata, adenocarcinomata and squamous cell carcinomata in the lungs of mice by the direct introduction of 1, 2, 5, 6-dibenzanthracene (designated by Pritchard as a carcinogen in cigarette smoke). This was done by pass-

ing silk thread coated with the carcinogen through the chest cavity by a needle, the thread being left in the lung.

Turning now to the indirect route, Murphy and Sturm (297) greatly increased the incidence of lung tumors without producing skin tumors by the repeated application of tar to a number of separate areas of the skin of mice. These experiments were confirmed by another investigator.

In 1935 Simonds and Curtis gave repeated intravenous injections to rabbits of a mixture of liquid petrolatum and tar known to possess carcinogenic properties and produced marked proliferation of the bronchial and alveolar epithelium and masses of granulation tissue showing areas of necrosis with gross vascular change, but no tumors.

Commencing in 1935 Andervont (3, 3-A, 481, 482, 483) and his associates carried out an extensive investigation into the experimental production of pulmonary tumors by subcutaneous injection. Using 1, 2, 5, 6-dibenzanthracene he produced lung tumors in about 45% of stock mice almost all of which were carcinomatous and transplantable. Other investigators have increased the incidence of lung tumors in mice by the injection of a 4% solution

of benzyrene in lard.

In 1939 Magnus himself took 125 stock mice and fed them a 0.4% solution of 1, 2, 5, 6-dibenzanthracene in olive oil. The solution was introduced into the stomach by the blunt end of a vaccine needle connected by rubber tubing to a hypodermic syringe. He originally set out to test this subject for its effect on the stomach but the mice began to die of lung tumors. He introduced carbon black and carmine in the same method and found slight traces of these substances in the lungs at autopsy. As the needle was being removed, small amounts of the solution were aspirated by the animals and found its way into the lungs. Of the 63 mice which survived the period of injections (20 months) 95.2% died with pulmonary tumors; 75% were malignant. The carcinogen not only greatly increased the incidence of benign bronchial papillomata but also doubled the incidence of malignant change in these tumors.

Because inhalation experiments were usually negative or inconclusive, Blacklock (2124) set out to determine if the lungs of Chester Beatty white rats would react to known carcinogens. He performed thoracotomies which exposed the lungs of the rats and injected 3, 4-benzpyrene directly into the lung. Five of the 6 rats developed sarcoma. When he used dead human tubercle

bacilli, 2 out of 4 rats developed sarcomas and when pellets of cholesterol and benzpyrene were pushed into the lung substance, 4 of 8 rats developed sarcoma, 1 an epidermoid carcinoma and 3 developed no tumors. However, Blacklock did produce one carcinoma and one sarcoma in 8 rats after injection of cigarette tar (4 cigarettes) in conjunction with dead tubercle bacilli.

Since 1939 the date of Magnus' paper, investigators have achieved some success in producing lung tumors by inhalation experiments. Campbell (1537, 1537-A) was the first investigator to successfully increase pulmonary tumors to a significant degree by the inhalation method. By 1942 he had already shown an increase in lung tumors when mice were exposed to tarred road dust, ground oxide of iron and precipitated silica. In addition he exposed mice 6 times a day 5 days a week for one year with the following substances:

1. Precipitated silica mixed with methylcholanthrene
2. Steel grindings
3. Alumina precipitated silica and ground oxide of iron in equal proportions
4. Radioactive dust from Czechoslovakia
5. Radioactive dust and calcium carbonite
6. Tarred road dust

All the dusts increased the incidence of lung tumors but not as much as expected. Hyperplasia also increased. Campbell feels that his mice might have become more cancer-resistant because the controls also showed a lower incidence of spontaneous tumors.

An experiment to test the effect of prior infectious diseases on lung tumor production in mice has shown negative results. Mice were exposed to human influenza virus type A and almost all mice became infected. The survivors were allowed to live out their life span after which they were autopsied. Although there was a marked degree of epithelial growth, no cancers, tumors, or even precancerous changes were observed. In fact an anti-carcinogenic effect was observed since the exposed mice had less tumors than the controls and the latent period of their tumors was longer. The authors state that although extrapolation is impossible, this experiment is inconsistent with the theory that influenza is a cause of cancer in man (1980-C).

Lung tumors have been induced by other methods. Creosote oil, a fairly well established carcinogen for man, caused lung papillomas and tumors when applied to the skin of laboratory bred mice. It was also determined by Roe et al. (3349) that mice living in wood cages treated with creosote had a much higher incidence of

pulmonary tumors than mice living in steel cages. Two rats developed squamous cell cancer of the lungs and 25 developed sarcomas.

Shimkin (cf. 1089) has achieved significant numbers of lung tumors with a wide variety of substances, injecting them subcutaneously.

The effect of dietary deficiencies was studied by Freedlander and French (2212) by altering the niacin content of the diet of strain A mice. One group of mice were given a niacin deficient diet and urethan, the second group a complete diet and urethan and the third a niacin deficient diet with no urethan. All mice were sacrificed after 4 months. The first group averaged 18.8 lung tumors, the second 10.8 and the third had negligible tumor formation. In another experiment 60 mice each were used in the following manner: One group maintained on a niacin deficient diet for 9 months, the second on a complete diet. The first group had 47% lung tumors and the second group 33%. The authors feel that depression of the niacin content for these mice led to biochemical disturbances contributing to carcinogenesis.

In another feeding experiment conducted by Mori and Yasuno (3717-A) pulmonary tumors were induced in female albino dd mice with isonicotinic acid

hydrazide. Tumors began to appear 134 days after beginning the experiment. The authors conclude that since the application of INH is very prevalent in treating tuberculosis in humans, it may be necessary to reconsider its use. Hyperplastic changes can also be induced by feeding this substance to rats and other animals.

As with the painting experiments, the experiments with regard to the production of lung tumors in animals present no clear-cut picture. Wynder (3525) believes the lungs of mice do not represent a good test organ since it is so difficult to induce lesions in their bronchi with even high doses of potent carcinogens. [Yet he is quick to attach significance to his mouse skin experiments.] However, as shown by the experiments discussed above, many investigators have been able to induce tumors and cancers in the lungs of experimental animals by inhalation of carcinogens (exclusive of cigarette smoke where results to date are all negative) as well as by other methods of introducing the carcinogen. In fact, Shimkin (1089) believes that the lungs of animals are particularly favorable sites for bioassay experiments because they are so sensitive to carcinogenic agents. Like the rest of the data regarding lung cancer there is both

2025018362

favorable and unfavorable material.

Also important caveats must be kept in mind in considering any lung tumor experiment. Some strains of mice exhibit a high sensitivity to a number of substances that will cause pulmonary adenomas or leukemia. These sensitive strains will develop pulmonary adenomas following the administration of any carcinogen irrespective of the route used -- skin painting, injection or inhalation. Inhalation experiments using such mice are misleading if they give the impression that similar results would be obtained in other species.

Also, it is important to know the spontaneous incidence of lung tumors in any strain of mice used. The higher the incidence, probably the more susceptible that strain is to the induction of lung tumors.

Inhalation experiments using cigarette smoke have given results which are difficult to interpret. For inhalation experiments in 1954, Essenberg, et al. (113, 115, 1615) employed strain A mice, which is a mouse strain showing a high incidence of spontaneous lung cancer. The incidence of pulmonary cancer (adenomas) in this strain was increased by exposure to cigarette smoke. Increased incidence of pulmonary cancer is produced in this strain by the administration

2025018363



of many known carcinogens by various routes, such as skin painting, subcutaneous injection, as well as by inhalation (1089). Experiments with a more resistant strain, e.g., C57 strain, have shown no pronounced pulmonary cancer development in the exposed animals. When Essenberg (115) used C57 mice, the mice all died from pneumonia with only three of the 40 test animals showing small tumors. Weller (722) exposed C57 mice to tobacco smoke for the duration of their life span without tumor development in any of the animals. Weller's results were presented in 1954. Campbell (1259), Mertens (282-A, 283) and Lorenz, et al. (268) also obtained negative results with cigarette smoke in inhalation experiments with mice. But Muhlbock (1029) did claim positive results in mice exposed to cigarette smoke.

Obviously, these discordant results present something considerably less than a definitive answer to the question whether inhaled tobacco smoke will cause lung cancer in animals. At the same time, it is dangerous to conclude that inhalation of tobacco smoke, perhaps by some methodology not yet employed, cannot produce lung tumors in some animals or strains thereof.

In any event, the tumor type observed in test mice is generally the adenoma. There is no known sig-

nificance between adenoma in mice and bronchogenic carcinoma in man. There is also no known correlation between the incidence of adenomas in these two species.

On the other hand, experiments conducted by Kotin, et al. (982-E, 2561-B, 3474), involving the inhalation by animals of polluted air of various types have yielded positive results. The inhalant used was "synthetic" exhaust gas from diesel and gasoline engines, which he had found to be very similar in composition to Los Angeles smog. Kotin selected for these inhalation experiments the oxidized aliphatic fraction of the exhausts or ozonized gasoline as opposed to the aromatic polycyclic fraction. This choice was prompted by the following reasons proffered by Kotin (3474):

1. This fraction represented a recently introduced atmospheric pollutant, the carcinogenic activity of which was demonstrated for the first time by Kotin in his skin painting experiments with motor exhausts.
2. This type of pollutant is present in greatest concentration in urban areas in contrast to rural areas. This corresponds with the results of epidemiological studies showing urban

areas to have the higher lung cancer mortality rate.

areas to have the higher lung cancer mortality rate.

3. Compounds chemically related to the oxidized aliphatic hydrocarbons have been shown to be carcinogenic to animals on injection by workers in Great Britain and the United States.
4. General agreement exists that the latent development period for lung cancer in the human is approximately 20 years; the oxidized aliphatic material was introduced into the atmospheric environment sufficiently long ago for any carcinogenic influence present to have become manifest at the time of the recorded epidemiological increases.
5. Technically, the synthetic reproduction of these materials in inhalation chambers is more feasible than is the use of aromatic polycyclic hydrocarbons adsorbed on soot.

Strain A mice, which have a high spontaneous pulmonary tumor incidence and presumably a low threshold of pulmonary reactivity to carcinogenic agents, were exposed to atmospheres of washed and unwashed ozonized gasoline; the latter he found to be roughly equivalent in composition to Los Angeles smog. Lung tumor produc-

V-A-61

2025018366

tion was observed in 24 percent of the animals treated with the washed atmosphere and 54 percent with the unwashed atmosphere. The washing process was designed to show that, whatever the carcinogenic agent is, it can be reduced. Many of the animals showed multiple pulmonary tumors. When C57BL mice, a strain possessing a low spontaneous pulmonary tumor rate and presumably a high resistance threshold to carcinogenic agents were treated similarly with these materials they gave 1.6 percent and 9.6 percent tumors respectively.

Two additional observations were made in this latter strain; namely, a consistent and often intense hyperplasia and metaplasia in the test animals as compared with the controls and a significant decrease in the incidence of extrapulmonary tumors in the test animals. These observed hyperplastic and metaplastic changes in mouse lung tissue should recall the similar findings of Auerbach et al. (870, 870-A, 1204-A, 2111) and Chang et al. (565, 900, 2068, 2158, 2486, 2752) with respect to human lung tissue at necropsy. These investigators claimed the changes were produced primarily by tobacco smoke. These investigations are discussed in detail in the section on pathogenesis. Another study, while reporting similar changes in human lung tissue on the basis of post-mortems, did not ascribe their produc-

V-A-62

2025018367

tion solely to tobacco smoke (2242) but to all assaults, e.g., respiratory infections, on lung tissue.

Earlier workers who had exposed various mouse strains to the exhaust fumes from motor vehicles did not obtain the tumor yields described by Kotin, et al. (3474). Smith (1969) in 1928 kept mice for six hours daily and three times a week in atmospheres containing fumes from an automobile engine. He obtained no tumors and concluded:

"Neither the experiments (with mice) nor the human cases give any support to the suggestion that carcinoma of the lung is caused by exposures to fumes of coal tar or gasoline."

Campbell (1259) exposed mice in inhalation studies to various types of dust over protracted periods and obtained pulmonary tumors with dust from tarred roads (71 percent). Exposure of the same strain of mice to motor exhaust gases, carbon monoxide and cigarette smoke did not yield an increase in pulmonary tumors in the test animals.

Whenever the inhalation of cigarette smoke is discussed, the positive findings of Essenberg using cigarette smoke are criticized and it is pointed out that Campbell conducted the same type of experiment with cigarette smoke many years ago and obtained negative results. Even though disagreeable, it must be noted that Campbell also conducted experiments similar to those described by

Kotin et al. using motor exhaust fumes and obtained negative results in contrast to those reported by Kotin et al. (3474) but mention is too often made only of his negative results obtained with cigarette smoke.

In other respiratory studies involving inhalation, Kotin et al. (3474) demonstrated that the ozonized gasoline produced total ciliary paralysis in the test animals and this paralysis had limited recovery after intense exposure. The cilia are minute hairlike protuberances found on many cells of the body, including the respiratory passages, which by movement protect the body from foreign substances and assist the removal of mucus. The authors also demonstrated a considerable degree of parallelism between alterations in this physiological function and cellular abnormality. This latter experiment should recall the work of Hilding (965, 965-A, 965-B, 1231, 1359) on the ciliary action of the lung of cattle (using India ink) and his statements on the proposed effect of cigarette smoke on the ciliary action in the lung. His theory was that cigarette smoke paralyzes the cilia at certain places in the lung thus facilitating the further deposition and retention of cigarette smoke and other suspected inhalants. He claimed substantiation of his theory by the results obtained with excess bovine lungs and cigarette smoke (see section on Pathogenesis).

In all of the foregoing experiments it should be borne in mind that the lung tumors produced in mice are different from the epidermoid or squamous cell carcinoma of the lung in man generally associated with environmental factors. The lung tumor in mice is usually adenomatous (1089) - that being the type of lung cancer in man for which the statistical studies have found minimum association. The reason for this is unknown, and the difference exists even though the lungs of both man and mouse are composed of the same type cells, namely epithelial cells.

Most cancer researchers are loath to admit that "mice are men" and vice versa and deplore the unqualified extrapolation of animal data to human experience. Even Wynder has stated (475) that "Animal data do not necessarily confirm or deny human data", although he did continue with the observation that ". . . historically much of our present understanding of carcinogenesis is based on corollary studies between clinical and laboratory research". He cited the clinical observation in 1775 of Pott (334) on "chimney sweep cancer" presumably caused by exposure to coal tar and soot; the animal studies of Yamagiwa and Ichikawa (476, 477) in 1915 demonstrating the carcinogenic activity of coal tar in the rabbit; and the chemical studies of Cook et

V-A-65

2025018370

al. (73, 74) in 1933 describing the isolation from coal tar of 3,4-benzpyrene. In this respect, Kotin et al. (3474) have recently echoed Wynder's sentiments on the correlation between animal and human data as follows:

"Laboratory investigation can contribute much information to the ultimate solution of (the pulmonary disease) problem . . . In the biological realm, strong supporting data can be secured, despite the fact that experimental investigations are necessarily limited to nonhuman animal species. It is necessary, of course, to remember certain deficiencies inherent in the biological studies. Choice of species, selection of appropriate animals, duration of exposure, concentration of test material, and routes of administration are all variables that modify the extrapolation of experimental data from other animals to man. Despite these shortcomings, past experience has shown a high index of meaningfulness of animal experiments for the human species. The broad spectrum of agents carcinogenic for visceral organs in experimental animals and apparently for those in man should make one proceed with caution in attributing the absolute dominance of any one agent over another."

The comments of Hartwell cited in the section on Biological Studies of Tobacco Smoke should also be recalled.

V-A-66

2025018371



#### 4. CHEMICAL STUDIES

As noted in previous sections, it has been contended by numerous authorities that air pollution has an adverse effect on the human organism, particularly with respect to its action on the lung and the induction of cancer in that organ. Since air pollution exerts such an adverse effect, it is presumed that some carcinogenic agent or agents in the air is responsible. Of the various classes of compounds showing carcinogenic activity the most important class is the polycyclic hydrocarbons. And 3,4-benzpyrene is probably the best known and one of the most potent members of this class. For the purposes of this discussion, we have assumed that the carcinogenicity of this compound in animals has been well established. If 3,4-benzpyrene has an adverse effect on human lungs, then the following data will show that man has ample opportunity to inspire this material and other similar injurious substances from the atmosphere in a quantity much greater than that from cigarette smoke.

V-A-67

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a. 3,4-Benzpyrene(i) Demonstration of its presence in various pollutants

From the first demonstration of the association between "chimney sweep cancer" and exposure to coal soot and coal tar by Pott in 1775 (334), various investigators had attempted to isolate a compound responsible for this type of cancer. These attempts gained added impetus in 1915 when Yamagiwa and Ichikawa produced tumors in rabbits by repeated application of coal tar (476, 477). In 1933, Cook et al. (73, 74) fractionated two tons of coal tar and isolated a carcinogenic compound subsequently identified by synthesis as 3,4-benzpyrene. The material isolated represented 0.003% by weight of the initial tar. The findings of Cook et al. were confirmed a year later by Winterstein et al. (468).

Since 1934, 3,4-benzpyrene has been identified in a host of materials in man's environment, and all of these materials to some degree contribute to air pollution, e.g., in coal tar by Berenblum et al. (35); in coal tar distillates by Berenblum et al. (30); in shale oil by Berenblum et al. (33, 34); in pitch by Hieger (172); in coal smoke by Goulden et al. (138); in diesel exhaust fumes by Johne et al. (2273), Kotin et al. (3474), Marterstock et al. (2316), and Commins et al. (2067); in the exhaust fumes from internal combustion

engines of the type used in automobiles by Kotin et al. (572, 669-A) (3474), Kuratsune (986), Goulden et al. (138) and Lyons and Johnston (1800-A, 2585-B); in rubber tire dust by Kotin et al. (119, 572, 669-A); in road tar by Kling et al. (235, 1740); as one of the products of incomplete combustion of gaseous, liquid and solid fuels by Tebbens et al. (1290, 2000); in wood soot and coal soot by Kuratsune (986); and in gas works effluents, industrial effluents and sewage by Wedgwood et al. (1125). The presence of 3,4-benzpyrene in cigarette smoke has been discussed at length previously.

It was suspected by Kotin et al. (237-B) that the 3,4-benzpyrene in the atmosphere was adsorbed on particulate matter, e.g., smoke particles, and did not occur free. This suspicion was substantiated by the findings of Commins et al. (3250) that 3,4-benzpyrene is not present in air in the vapor phase.

The evidence supporting the presence of 3,4-benzpyrene in air pollutants to which man is exposed is quite substantial. The proof that this material, in addition to other suspected carcinogens, e.g., arsenic, does reach the human lung was provided by Sula (3204) who demonstrated the presence

of both 3,4-benzpyrene and arsenic in the anthracotic nodes of human lungs at autopsy. Recently, Falk et al. (2517-A) summarized the meaning of the findings with respect to the polycyclic hydrocarbons (including 3,4-benzpyrene) in the atmosphere. They noted that various polycyclic hydrocarbons, known to be carcinogenic in animals, were present in the atmosphere; these carcinogens were adsorbed on soot particles; and at least one of these, 3,4-benzpyrene, was eluted rapidly compared with the noncarcinogen, pyrene, from the soot particles in the lung. These findings were based on post-mortems done at various times after death. Thus, we have the demonstration of (a) the presence in air of a known (and potent) carcinogen in substantial amounts adsorbed on soot particles; (b) the presence of this material at the site of injury, e.g., the lung; and (c) a mechanism whereby the active material may be eluted from the soot and thus exert its action on the cellular components of the tissue. In addition, we have proof of the many sources of this presumably injurious compound.

Another important piece of evidence was the demonstration by Miescher et al. (284) that the

V-A-70

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carcinogenic activity to skin of mice of the tar and smoke from the air of a number of Swiss towns was directly proportional to the 3,4-benzpyrene content of the smoke studied.

V-A-71

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(ii) Demonstration of the Presence of 3,4-benzpyrene  
in the Atmosphere of Various Areas

Cooper et al. (76, 77) demonstrated the presence of 3,4-benzpyrene in the atmosphere of the town of Salford, England, and showed that its changes in concentration were seasonal. During the winter months when the quantity of domestic smoke increased, the amount of 3,4-benzpyrene also increased (1559). A similar study was described by Waller (456) in 1952. He found the following:

(1) The concentration of 3,4-benzpyrene rises markedly during the winter months.

(2) The mean average values for this compound increase in proportion with the size of the town.

Campbell and Clemmesen (1358) studied the 3,4-benzpyrene content of the atmospheres of Birkenhead (a large industrial town), Hoylake (a small town) and Tattenhall (a rural district) in England. They noted the maximum concentration of this material during the winter months, the minimum concentration during the summer months and a gradation in concentration proportional to the degree of urbanization.

V-A-72

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In the United States, numerous studies have been reported in which it has been demonstrated that 3,4-benzpyrene is present in both rural and urban atmospheres. Cholak (cited by Chambers et al. (1544)) gave values for the 3,4-benzpyrene content of the atmospheres above the following cities: Atlanta; Boston; Charleston, W. Va.; Chattanooga; Chicago; Cincinnati; Fort Worth; Houston; Los Angeles; Louisville; Minneapolis; New Orleans; New York; Philadelphia; Portland; Providence; Salt Lake City and San Francisco. Kotin et al. (237-A) and Duboff (1344) have conducted extensive studies on the 3,4-benzpyrene content of the Los Angeles atmosphere; Sawicki et al. (1422) have done the same for Cincinnati.

Besides the United States and the United Kingdom, comparable studies have been conducted in other countries, e.g., Italy, Norway, and the U.S.S.R. D'ambrosio et al. (905) and Sirtori (2393) determined the 3,4-benzpyrene content of the atmosphere above Palermo and Milan, Italy, respectively. Campbell and Kreyberg (2153-A) reported a study conducted in Norway where the 3,4-benzpyrene content of Oslo and eight small

V-A-73

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Norwegian towns was determined. The values for Oslo were much greater than those for the towns; the winter values in all cases were higher than those for the summer.

Considerable emphasis has been placed on air pollutants as a cause of lung cancer by the Russian scientists and we have several interesting points arising as a result of their studies. According to Shabad (cited by Shimkin et al. (1187)) the high lung cancer incidence in Leningrad and Moscow is attributed directly to the high concentration of air pollutants in these two cities.

Dikun et al. (917) studied the 3,4-benzpyrene content of snow collected at a distance of 2.5 km. from a particularly troublesome factory in Leningrad and found 0.01 mg. per square meter. The comparable values for all of Leningrad ranged from 0.2 to 7.8 mg. per square meter. It was calculated for a particular area in Leningrad comprising a highly industrialized neighborhood that 200 grams of 3,4-benzpyrene per square kilometer would be deposited in a given six-month period. This is equivalent to the amount of 3,4-benzpyrene in the mainstream (inhaled) smoke of 10 trillion cigarettes.

Shabad (3029) found that the 3,4-benzpyrene content of the atmosphere above cities and towns in Russia increased with the increased smoke content;



was highest in the industrial areas, low in the rural areas, and nil in Angarsk; and showed, everywhere but Angarsk, the seasonal variation described by other workers (see above). Angarsk is a new city recently built in Russia and does not use conventional heating. As described by Shahbad (2886), the heating system is "revolutionary".

Grushko et al. (3126) analyzed the atmosphere above Irkutsk and Angarsk, two cities of comparable size and degree of urbanization. Irkutsk employs conventional heating techniques; Angarsk, the new method. The latter gave no 3,4-benzpyrene in the atmosphere, whereas Irkutsk gave a fairly high value.

Stocks and Campbell (1104-A) have calculated the amount of 3,4-benzpyrene inspired per year by a resident in an urban, a mixed, and a rural area in England. The values obtained were 450, 157, and 41 micrograms respectively. Contrast these values with the amount taken in by a pack-a-day inhaling smoker, i.e., 146 micrograms per year (using a value of 2 micrograms in the mainstream smoke per 100 cigarettes). Other studies showing high concentrations of 3,4-benzpyrene in the atmosphere have not related these to the annual human intake. It should be borne in mind that one of the contributors to the 3,4-benzpyrene content of the air is the sidestream (not inhaled) smoke of a burning cigarette. This amount, however, is probably insignificant

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V-A-75

b. Other Polycyclic Hydrocarbons

Although the major emphasis has been placed on 3,4-benzpyrene in the studies of air pollutants conducted during the past 36 years, these atmospheric pollutants do contain other carcinogenic polycyclic hydrocarbons. 1,2-Benzpyrene, a known carcinogen somewhat less potent than 3,4-benzpyrene, has been found in commercial rubber by Falk et al. (119), in automobile exhausts by Lyons and Johnston (2585-B), and in the atmosphere by Kotin et al. (237-A) and Shore et al. (1091). 1,2,5,6-Dibenzanthracene, a very potent carcinogen, is suspected as a product of incomplete combustion of solids, liquid and gaseous fuels (2000).

3,4,8,9- and 3,4,9,10-Dibenzpyrene, both highly potent carcinogens have been found recently in coal tar by Buu-Hoi (3243) and Schoental (2095) respectively.

c. Oxidized Aliphatic Compounds

A new class of carcinogenic compounds has recently been described by Kotin et al. ((3474) and references cited therein). This class of compounds is present in the Los Angeles atmosphere and can be produced "synthetically" in the laboratory either from a gasoline engine or by treatment of gasoline with ozone. Chemical and physical comparisons of the material from these three sources indicate substantial agreement in composition. The composition of this material is not, as yet, too clearly defined but it is suspected that aliphatic peroxides, peracids and epoxides constitute the mixture. It is carcinogenic both to animal skin and lung (see Biological Studies). The concentration of this material is very high in Los Angeles and very low in a neighboring desert area (3474).

Note that numerous authorities (see Introduction to this Section V) have distinguished between the type of air pollution represented by Los Angeles smog, which is said to be generated in large part by vehicular exhausts containing oxygenated aliphatic hydrocarbons as well as the polycyclic hydrocarbons, and the apparently more usual form of pollution found in other parts of the United States and in Europe,

V-A-77

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characterized by the effluents of soft coal combustion of which 3,4-benzpyrene is frequently assumed to be the most noxious. We point this out to caution against over-emphasis of the results presented by Kotin.

V-A-78

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d. Nitrogen Oxides

Both contaminated air and cigarette smoke contain various oxides of nitrogen, e.g., nitrous oxide, nitrogen dioxide, nitric oxide (see Introduction to the Section V), and the suggestion has been recently proffered that these compounds may be carcinogenic, but biological evidence of carcinogenicity is not available to date (cf. (3828)).

V-A-79

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## 5. SUMMARY

1. Epidemiological studies have indicated a greater incidence of lung cancer among urban residents than among rural residents.

A. This so-called urban excess has been disclosed in some of the statistical studies (of both the retrospective and prospective types, comparing lung cancer victims and their smoking habits with a control population) conducted to discover any relationship between smoking and lung cancer.

(1) Hammond and Horn (253<sup>1</sup>-B): Death rates due to cases of bronchogenic carcinoma (exclusive of adenocarcinoma) said by the authors to be well established were found to be higher in urban than in rural areas. However, cigarette smoking was held to be more common among city dwellers than among men in rural areas. Adjusting for smoking habits, age and area of residence the rate was still 25% lower in rural areas than in large cities. Hammond and Horn concluded that this difference could be due to some factor producing lung cancer associated with city life (cf. Stocks et al. (1104-A)) or to better case finding and diagnosis in cities than in rural areas (cf. Rigdon); however, the authors claimed that their

V-A-80

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data prove that whatever this urban factor may be, its effect on lung cancer death rates is small compared with the effect of cigarettes.

(11) In a companion paper (2534-A) relating to death rates from all causes Hammond and Horn compared data for smoking habits, age and residence, and concluded that about 3/5 of the difference in age-standardized death rates found by them between rural and urban populations disappeared when smoking habits were equated. Using their figures with respect to total death rates, it is apparent that 2/5 of the difference must be due to some urban factor, but they fail to concede this in so many words, although recognizing that rural death rates in the United States "generally tend to be somewhat lower than death rates in cities".

(111) In Doll and Hill's retrospective study (103) published in 1952 they compared lung cancer incidence, urban and rural death rates, and smoking habits. They claimed to have found both a greater lung cancer mortality in Greater London and more cigarette smoking. They concluded, however, that the recorded differences in mortality between city and country were greater than could be attributed wholly to differences in smoking habits. Of the various etiologic factors studied (i.e.,

occupation, social class, etc.) only place of residence was found to have an association with lung cancer mortality.

(iv) Doll and Hill retreated from this position in a later paper on their large scale prospective study of doctors in England ( 918-D) published in 1956. There they claimed that the differences between urban and rural smokers and nonsmokers in the matter of lung cancer mortality, and similarly between urban and rural light, medium and heavy smokers could not be explained in terms of a differential exposure to atmospheric pollution which happened to be associated with smoking habits. This claim is contrary to that of Stocks and Campbell (1104-A) (see infra).

(v) Stocks and Campbell (1104-A) conducted a survey of segments of the populations of cities, mixed areas and rural areas in England and Wales in which they compared death rates from lung cancer with smoking habits and with the amount of 3,4-benzpyrene determined in the atmosphere. They claimed a correlation between rural death rates from lung cancer and the number of cigarettes smoked per week. Liverpool rates exceeded rural rates in every category, but declined from an urban-rural ratio among nonsmokers of 9:1 to a ratio approaching

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unity among heavy smokers. Nevertheless, the absolute urban excess was approximately the same in each smoking group (except that for heavy smokers), suggesting that an urban factor was added to the smoking effect. In their opinion smoking would account for  $1/2$  the urban deaths while  $3/4$  of the remaining  $1/2$  would be attributable to a factor "which is only slightly present in the rural area".

In searching for this factor they suggested that 3,4-benzpyrene perhaps plays a dual role through cigarette smoke and in air pollution. They based this suggestion on the estimates of the combined intake of 3,4-benzpyrene per year from the air and from cigarettes. Their measurements showed that the concentration of 3,4-benzpyrene increases with industrialization and in Liverpool the amount of 3,4-benzpyrene was eight to eleven times that in rural areas, which is a ratio roughly corresponding to the difference found by them between death rates in Liverpool and rural areas for nonsmokers (929).

(vi) Placing blame on 3,4-benzpyrene gives the opposition the opportunity to claim a concession since 3,4-benzpyrene is a known ingredient of cigarette smoke (although Wynder himself has refuted the idea that there

V-A-83

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is a sufficient quantity present in cigarette smoke to cause lung cancer). One can argue that Stocks and Campbell are wrong in their selection of 3,4-benzpyrene as the culprit, but correct in finding an urban factor. See infra for other possible harmful ingredients of the atmosphere and cigarette smoke.

(vii) In a study of lung cancer and bronchitis mortality and their relation to atmospheric deposit and smoke in England and Wales published in 1959, Stocks (3804) claimed that standardized mortality ratios for lung cancer are related to the average amounts of smoke in the air. The data indicated that lung cancer was significantly correlated with smoke but not with deposit (and, parenthetically, the reverse with respect to bronchitis). This finding may be of particular importance in the light of the experiments of Kotin et al. with atmospheric pollutants. Two diseases for which the urban excess is pronounced are bronchitis and lung cancer. Note that some authors consider a previous history of respiratory diseases as a contributing factor to lung cancer. Note also Stocks' forceful comment that bronchitis and lung cancer are particularly high in England as is the amount of air pollution from domestic chimneys. The urban excess is smaller in countries where coal is little used for

domestic heating purposes. Coal usage in the United States has been fairly constant over the past 50 years.

B. Other studies, measuring residence, mortality and in some cases smoking habits without a specific control population, have also found an urban excess.

(i) Hoffmann and Gilliam reported in 1954 the results of a study of age, race, sex and residence (urban-rural) specific rates for mortality attributed to lung cancer for the United States for an average of the years 1948-9 based on vital statistics. In all age, race and sex components they found the rate greater for urban than for rural residents. There are other studies of the same type to the same effect.

(ii) It seems obvious that the studies in (i) above are meaningful only if smoking habits are the same in urban and rural populations. Haenszel, Shimkin and Miller for the United States and Stocks and Campbell for Great Britain have presented data purporting to indicate that smoking is more pronounced in urban populations. Greene has asserted (without documentation) that country people smoke as much, if not more, than do city people. Cornfield et al. (3409), relying on Haenszel, Shimkin and Miller, answer that this assertion is not borne out by the facts.

V-A-85

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(iii) Vital statistics are founded upon death certificate diagnoses and are thus open to the same type of objection directed to the statistical studies linking lung cancer and smoking. On the other hand, the tobacco theorists are effectively stopped from raising this point.

C. Cornfield et al. (3409) concede the existence of an urban excess. They claim that an urban factor is additive to cigarette smoke, and that the urban factor accounts for only a fraction of the urban-rural difference. They claim also that urban smoking habits are less moderate than rural.

2. The urban excess points to some factor not found in rural areas (or found only in small amounts) and unrelated to smoking, which is responsible for the excess risk. The most likely urban factor is polluted air from industrialization (although Clemmesen et al. (70,1552-C) disagree).

A. Industrialization can be the urban factor only if (a) there has been a real rather than an illusory increase in lung cancer and (b) there has been an increase in industrialization accompanying the increase in lung cancer incidence. Note, however, that to argue that the evidence establishes a real increase in lung cancer is

to concede one of the premises necessary to incriminate tobacco.

B. Industrialization of the United States and other western countries has progressed rapidly and dramatically during the past half century, simultaneously with the marked increase in recorded lung cancer incidence in those countries. The increase in industrialization is obvious. In addition, evidence of it is found in the increased usage of certain concomitants of industrialization, such as motor vehicles, fuel oil, and asphalt highways. These factors have been shown capable of emitting substances suspected of being harmful to man.

(1) The late Dr. Kennaway points out, however, that notwithstanding increased industrialization there have been rather effective steps taken to curb the ill effects of atmospheric pollution, such as the more economical combustion of smoke-producing fuels, and the replacement of these fuels by coal gas and electricity. He gives as an example of the efficacy of these measures, the fact that Pittsburgh has been converted from an extremely dirty city to one of the cleanest. It appears to us plausible that whatever remedial measures have been taken to combat atmospheric pollution they must be insignificant in terms of the manifest gigantic growth of industry.

(ii) Cornfield et al. (3409) contend that the population exposed to established industrial carcinogens (e.g., chromates and coal gas) is small; and therefore these agents cannot account for the increasing lung cancer risk in the remainder of the population. See Kotin (786-A) for the proposition that such industrial carcinogens have a cumulative effect in the pollution of community-wide atmosphere. It is important to point out that the concept of atmospheric pollution as a cause of lung cancer, advanced here, is to be differentiated from exposure to what we call (in agreement with Hueper, among others) occupational carcinogens. The latter are the industrial carcinogens described by Cornfield et al., and are concededly in contact with a relatively small segment of the population. In their paper organizing the arguments in favor of the cigarette smoking theory of lung cancer causation, Cornfield et al. do not even pay lip service to the possibility of injurious pollution of the atmosphere by the various impedimenta of industrialization. The point is that many persons are exposed to atmosphere polluted by industry and by the exhausts of cars and domestic furnaces even though not working in factories.

(iii) The claim that atmospheric pollution is respons-

ible for lung cancer must contend with the demonstrated male-female disparity. Some adherents to the smoking-lung cancer theory (see Cornfield et al. (3409)) urge that the two or three decade head-start that males have over females in respect of lung cancer incidence corresponds to the time difference in acquisition of the smoking habit; Cornfield et al. cite Haenzsel, Shimkin and Miller (1156) as authority for the proposition that men on the average have been smoking for longer periods than have women. Kotin (982) maintains that the difference in incidence is equally consistent with the experience of the sexes in exposure to atmospheric pollution. His argument, and that of others, such as Hueper, is that women only to a very limited degree in the past have worked in manufacturing installations, have driven in heavy traffic to and from work, and have performed heavy manual labor in dirty polluted environments. The inference from both arguments is that the difference in the lung cancer incidence between the sexes should decrease with time. At present the disparity has shown no inclination to decrease despite the absolute increase in incidence among each sex (Hueper 970-B).

(iv) The position of Cornfield et al. (3409) derives support from the observation that the sex differences in tobacco use were especially pronounced at ages over

55 when most lung cancer deaths occur. In this age group 0.6 per cent of American females have been reported as current users of more than one pack of cigarettes daily compared to 6.9 per cent for men, as shown by Haenzsel et al. (1156). Comparable data have been presented in England (2690-A).

(v) Atmospheric pollution is a possible explanation for the fact, for which the smoking-lung cancer theory has no explanation, that most heavy smokers do not get lung cancer and some non-smokers do. Macdonald (2084), Eckardt (924) and Little (2082) have forcibly made the point that most heavy smokers do not contract the disease while some non-smokers do. A weakness of the foregoing explanation is the possibility that non-smokers may be exposed to whatever harmful ingredients tobacco smoke may contain by inhalation of the air in smoke-filled rooms. (See Harmsen and Effenberger (2535) and letter to the editors of LANCET by Gordon (2228)). Another weakness is the fact that the explanation does not refute the possibility that smoking and atmospheric pollution have a cumulative, synergistic or cocarcinogenic effect. An attempt to advance the theory that tobacco smoke is anticarcinogenic to the effect of air pollutants would be met by the statistical studies involving smoking

V-A-90

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and residence.

3. The biological evidence in support of the carcinogenic activity of air pollution in skin painting experiments is paralleled, of course, by the biological evidence in support of the carcinogenic activity in skin painting experiments of condensed tobacco smoke. Several major differences are apparent, namely, the quantities employed in the tobacco smoke studies are much greater than in the case of the other environmental factors and there are numerous reports in the scientific literature in which carcinogenesis could not be demonstrated using tobacco smoke.

In respect of inhalation studies, the evidence in support of certain air pollutant factors is quite overwhelming when compared with results of inhalation studies using tobacco smoke.

It may be argued by the proponents of the lung cancer-cigarette smoking theory that tobacco smoke in conjunction with other environmental pollutants leads to a synergistic effect such as has been recently claimed by Suntzeff et al. (3807) in the case of tobacco smoke and B-radiation. Another attack possible is that the proponents of the lung cancer-smoking theory might willingly concede the pronounced carcinogenicity of

V-A-91

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various air pollutants but submit the claim that this effect is markedly enhanced by the carcinogenic activity of tobacco smoke. This latter claim has been made recently by Gellhorn (2780) on the basis of skin painting experiments with mice combining 3,4-benzpyrene and tobacco smoke condensate.

One danger inherent in reliance on the biological studies incriminating air pollutants in lung cancer causation is that the type of evidence in support of this factor as an etiologic one is almost identical, with the exceptions noted, to that incriminating tobacco smoke. Any attempts to transfer the blame for the present high incidence of lung cancer on the basis of the biological evidence might be construed by the anti-smoking faction as a tacit admission that we accept as valid the results of such biological studies, no matter what factor, i.e., air pollutants, tobacco smoke, etc., was studied. Perhaps the best use of the evidence pointing to air pollution as a guilty party is by way of showing that it is unreasonable and unsound to address one's attention solely or even primarily to cigarette smoking in seeking the cause of lung cancer in view of the controversial and inconclusive evidence applicable to each. In fairness to cigarette smoking,

V-A-92

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however, it is apparent that at present the evidence against air pollution is stronger than that against smoking.

4. On the extrapolation issue, it is of course obvious that one cannot predict the reaction of the human body on the basis of animal experiments, and it must be pointed out that one cannot treat the skin painting experiments in animals using atmospheric pollutants as evidence of the results to be anticipated in man without also extrapolating to man the skin painting experiments on animals using cigarette smoke. It is clear, by the weight of scientific opinion, that animal experiments are considered of some value in predicting man's reactions, and the fact is that many of the industrial materials carcinogenic to animals have also been carcinogenic to man.

5. Chemical studies contribute the following to the picture of the role of air pollutants:

A. Atmospheres contain at least three classes of compounds known to be carcinogenic to animals. Bearing in mind the dangers inherent in extrapolation from experimental animals to man, it is pre-

V-A-93

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sumed by many authors that these compounds are not beneficial to man.

B. Many sources of these injurious materials have been documented.

C. The concentration of these materials is higher in urban than in rural areas as is the incidence of cancer of the lung. Also, the concentration of these materials is generally proportional to the degree of urbanization. Similar findings have been reported in this respect for lung cancer incidence.

D. At least two suspect compounds, 3,4-benzpyrene and arsenic, are known to reach the site affected, i.e., the lung, although it is as yet not known whether either 3,4-benzpyrene or arsenic has any adverse effects on the human lung.

E. The highly potent 3,4-benzpyrene, adsorbed on soot particles, after reaching the human lung, is said to be rapidly eluted from the soot in contrast to less active materials such as pyrene.

F. The carcinogenic activity (in animals) of various effluents is proportional to the 3,4-

V-A-94

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benzpyrene content.

G. The concentration of the carcinogenic polycyclic hydrocarbons, arsenic, and the oxidized aliphatic compounds in air pollutants is much greater than in tobacco smoke. In fact, the latter class of compounds has not been detected in tobacco smoke to date.

V-A-95

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COMPELLED PRODUCTION

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COMPELLED PRODUCTION

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SMOKING AND HEART DISEASE

A Review of Research Grants

Supported by the National Heart Institute

July 1, 1949 to June 30, 1962

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by

May Sherman, M. D.

Extramural Programs

National Heart Institute

National Institutes of Health

Bethesda 14, Maryland

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Table of Contents

INTRODUCTION.....	1
THE AGENT: TOBACCO SMOKE.....	3
EXPERIMENTAL STUDIES.....	4
Heart and Coronary Circulation.....	5
Peripheral Circulation.....	8
Blood Lipids.....	11
Pulmonary Function and Disease.....	12
Neurohormones and Human Behavior.....	18
The Fetus.....	23
Ballistocardiography and Electrocardiography.....	25
Carbon Monoxide.....	27
OBSERVATION OF POPULATION GROUPS.....	29
Retrospective Approach.....	30
Prospective Approach.....	33
Cooperative Studies.....	33
Ethnic and Migratory Influences.....	35
Community and Socioeconomic Influences.....	39
Genetic Influences.....	41
EPILOG.....	45
REFERENCES.....	49

2025018404

## INTRODUCTION

Does tobacco smoking have ill effects upon human health? This question--asked innumerable times, by scientist and layman, over the past few decades--has not yet received a definitive answer. In 1957, a Study Group on Smoking and Health,<sup>26</sup> organized at the suggestion of the American Cancer Society, the American Heart Association, the National Cancer Institute, and the National Heart Institute, prepared a statement of the known facts and made recommendations for further research. In the past few months, public interest in the potential health hazard of smoking seems to have flared again, mainly because of new statistical, experimental, and postmortem evidence--the first two associative, the last complicated by host and dose vagaries, and none of it definitive. A kind of vicious circle--scientific evidence; public concern; counter-evidence from the tobacco industry; more research and new scientific evidence--seems alternately to submerge and to buoy the human penchant for smoking. Two sets of circumstances--that associations may be wrongly interpreted as cause and effect and that experimentally active doses may merely reflect the propensity of any substance to be toxic under suitable circumstances--may be the trees now obscuring the forest of truth.

- 2 -

The literature on the health effects of smoking is already voluminous. In the pages that follow an attempt is made to summarize research on smoking supported now and in the past by the Extramural Programs of the National Heart Institute. By no means a review of U.S. or world literature on the subject, this summary merely complements similar reviews prepared or contemplated by other investigative groups in the United States--particularly, the American Cancer Institute, the American Heart Association, the Committee on Tobacco and Health of the New York State Academy of Preventive Medicine, the Tobacco Industry Research Committee, the Division of Air Pollution of the Public Health Service, the National Cancer Institute, and direct research units of the National Heart Institute itself. That such reviews from these various groups will be forthcoming seems inevitable in view of recent interest expressed in the problem by the Surgeon General of the Public Health Service and by the American Medical Association. It is hoped that the effort that these pages represent will help round out a larger story.

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## THE AGENT: TOBACCO SMOKE

Some 200 compounds have been identified in tobacco and almost 300 in tobacco smoke. About 60 per cent of those present in the smoke have not been found in the tobacco plant and are believed to be formed during combustion. Only a small number of these compounds have been subjected to quantitative study. Because isolation procedures are laborious and the information obtained is woefully incomplete, the possibility was raised that some of the compounds might be artefacts, stimulating a recent reinvestigation<sup>18</sup> of precipitation procedures used by earlier workers to isolate cigaret smoke alkaloids.

It is said that most of the components of tobacco smoke are absorbed in amounts too small to have acute pharmacologic effects or to permit their detection in the body after inhalation; but information about possible long-term or cumulative or synergistic action is sparse. Of the components that have probably received most attention--the carcinogenic aromatic hydrocarbons, the oxides of nitrogen, hydrocyanic acid, carbon monoxide, and nicotine--only the last 2 are of immediate cardiovascular interest. Since the known pharmacologic effects of smoking are attributed entirely to the nicotine content of tobacco, studies of smoking and of nicotine are discussed together under the various headings of this review. The few grants concerned with the toxicology of carbon monoxide are considered separately.

## EXPERIMENTAL STUDIES

The pharmacology of nicotine is known to be highly complex. How much more complex, then, are the conjoined biologic effects of all the components of tobacco smoke! Nicotine affects the body through many systems, and in a given species its several actions on the same system or receptor may be in diametric opposition depending on the dose, the route of administration, the presence of habituation, and the physiologic integrity of the subject. Much apparently contradictory evidence stems from this phenomenon. It is not intended to review the biologic activity of nicotine here, but merely to relate what has been discovered or confirmed under National Heart Institute support. The changes to be described are by and large acute changes, probably lasting for less than an hour, and cannot be interpreted as having any relationship to the possible effects of chronic exposure over a period of years.

The conflicting actions of nicotine were recently reviewed by an investigator:<sup>36</sup> In low doses nicotine stimulates sympathetic ganglia and adrenal medulla, producing all the known effects of sympathetic stimulation, including increase in the rate and force of cardiac contraction, vasoconstriction, and hypertension; and parasympathetic ganglia, producing the

- 5 -

reverse effects. By means of carotid and aortic chemoreceptor reflexes acting through the efferent sympathetic nervous system, nicotine produces hyperpnea and circulatory stimulation distinguishable from that produced by its direct action upon sympathetic ganglia only by the smaller dosage required for the former; but by means of pulmonary and coronary chemoreceptors, it produces apnea, bradycardia, vasodilation, and hypotension. Secondary compensatory changes may complicate and contradict any of these primary effects. In higher concentrations most or perhaps all of these actions can be reversed or blocked. Other pharmacologic effects on skeletal muscle, sensory receptors, and the central nervous system, often with conflicting manifestations, are known. Human beings may--like animal subjects--show individual variability in response; may become tolerant of nicotine; or may respond in an unexpected fashion because of surgical procedures, particularly those performed on the sympathetic nervous system.

#### Heart and Coronary Circulation

Smoking produced<sup>58</sup> both in normal volunteers and more so in patients with coronary disease an increase in heart rate, systemic arterial pressure, and left ventricular work. Although in an earlier study<sup>58</sup> a significant rise in coronary blood flow occurred in normal subjects, neither group in the present series had a significant change in coronary flow, and myocardial oxygen consumption was about the same as before smoking. The various neurohumoral responses that smoking elicits might, however,

2025018409

- 6 -

modify myocardial oxygen uptake unpredictably. Although coronary subjects showed no evidence of myocardial ischemia, it was conceivable that an enhanced ratio of left ventricular work to oxygen uptake could, if large enough, produce ischemic symptoms in such patients. Others<sup>63</sup> noted that smoking induced a decrease in coronary blood flow and diminished delivery of oxygen to the myocardium in patients with angina pectoris, but none of the patients developed angina during inhalation. When epinephrine and pitressin were administered<sup>63</sup> simultaneously to dogs, in approximately physiologic doses, pitressin limited the increase in coronary flow expected from epinephrine, suggesting that endogenously released pitressin may affect the coronary response to smoking.

When open-chest dogs inhaled from 1,200 to 1,500 ml. of nonfiltered cigaret smoke over a period of 30 seconds by means of a specially calibrated smoking device, increases occurred in blood pressure and cardiac output, resulting in increased cardiac work.<sup>19</sup> When the increase in cardiac work had reached a maximum, a fleeting decrease in coronary arteriovenous oxygen differences resulted in decreased myocardial oxygen utilization despite the rather marked increase in coronary flow. This was followed by prolonged increase in coronary arteriovenous oxygen differences and sustained increase in cardiac oxygen utilization. As suggested by extreme electrocardiographic alterations, such effects were considered detrimental to adequate cardiac function.

2025018410

- 7 -

In a study of cardiac metabolism, investigators<sup>11</sup> measured coronary blood flow, cardiac utilization of oxygen, glucose, lactate, and pyruvate, and left ventricular work in anesthetized healthy young dogs with normal coronary arteries receiving intravenous infusions of nicotine in doses intended to increase the heart rate and left ventricular work. When nicotine was given at a dose of 5 mcg./Kg./min. for a total dose of 4 mg.--selected because it was considered the equivalent of smoking 1 standard cigaret--no statistically significant changes were noted in heart rate, arterial pressure, or respiration. When nicotine was given at the rate of 15 mcg./Kg./min. for a total dose of about 20 mg., cardiac arrhythmia, a drop in blood pressure, and respiratory failure occurred. With the total dose lowered to 12 mg.--equal to perhaps 3 standard cigaretts--the blood pressure rose to varying degrees, then fell sometimes to below preinfusion levels, although the nicotine was still being infused. The heart rate increased, then diminished as the pressure still increased, then accelerated once more to a peak, finally returning to base levels usually within 10 minutes after the infusion ceased. The average heart rate increased from 66 to 115, but no significant increases in blood pressure or in left ventricular work--the intent of these experiments--were produced. Changes in coronary blood flow were inconsistent. Significant changes in coronary oxygen arteriovenous differences, myocardial oxygen extraction, and coronary sinus venous oxygen

2025018411



- 8 -

tension were not observed. Higher nicotine dosages tended to stimulate respiration and induced an increased arterial oxygen content. The results appeared to support the contention that coronary blood flow after the experimental administration of nicotine increases enough to meet the metabolic need for oxygen, perhaps through central nervous system pathways, so that myocardial oxygen extraction need not be increased to meet the increased contractile vigor. But if the arteries are so fixed by sclerosis that their tonus cannot change, increased contractile force calling for a greater oxygen supply may find the coronary flow inadequate and result in relative coronary insufficiency. Thus smoking in a patient with coronary artery disease may precipitate an attack of angina.

#### Peripheral Circulation

Smoking probably owes much of its appeal to the effects of nicotine upon the peripheral circulation, its vasoactive potency providing a sensation of stimulation and physical well-being that the user misses when he gives up the smoking habit. Yet the effects of nicotine upon the peripheral circulation are not clear cut, and the conflicting results reported probably are the result of differences in concentration and route of administration, in recipient species, and in the physiologic or pathologic status of the recipient. Thus, smoking or the intravenous injection of nicotine will constrict some but not all vessels in the skin and will increase blood flow in skeletal muscle; but the intra-arterial injection of nicotine into a cat's gastrocnemius muscle produces

2025018412

- 9 -

both vasoconstriction and vasodilation. Preexisting vascular tone seems to determine the response.

Injected intra-arterially and intravenously into a cat's active hyperemic muscle, nicotine produced no further increase in flow; if the dose was large enough, vasoconstriction occurred.<sup>60</sup> Later, as blood flow slackened during continued activity, nicotine produced a transitory increased flow. Infused continuously into an artery, nicotine induced a progressive diminution in flow. In man, the changes in peripheral blood flow are even more unpredictable because they seem to be complicated by psychologic factors, neuromuscular effects, peripheral effects secondary to the elevation of blood pressure, and the release of catecholamines from the adrenals.

In doses believed comparable to those reported in the blood of smokers, nicotine alone or synergistically with ineffective doses of vasopressin produced significant decreases in the vasa vasorum flow of isolated surviving swine arteries.<sup>8</sup> If such a change also occurs in living human beings, it provides an additional effect that must be included among all the other peripherovascular possibilities.

The fact that a multitude of forces can act upon a peripheral site probably explains why in 24 of 44 servicemen smoking induced a delay or decrease in vasodilation of peripheral skin vessels, in 10 it induced no change, and in the remaining 10 it increased or hastened vasodilation.<sup>60</sup> If peripheral changes in a given subject could be shown to be fairly consistent, an explanation

2025018413

- 10 -

might be forthcoming of why the smoking habit is welcomed in some and rejected in others.

Is venous tone affected by smoking, and if so, how are these effects mediated? Examining venous tone in the extremities by means of a plethysmographic method, investigators<sup>21</sup> are noting man's venous response to a number of stimuli, including nicotine. Observing that in men who smoked the resting volume of the extremity diminished, these workers obtained venous pressure-volume curves from the forearms of healthy young habitual smokers before, during, and after the intravenous injection of a single dose of nicotine or after infusion of 0.5 to 4.4 mg. at a constant rate over a 10-minute period. The injection of 1 mg. of nicotine or the infusion of doses larger than 3.4 mg. within 10 minutes regularly produced an increase in venous tone. Circulating epinephrine did not appear to be an important factor, because the response could not be altered by the intravenous administration of phentolamine in a dose that can modify the venous response to epinephrine infused at the rate of 15 mcg./min. Nicotine might have been acting centrally, since pain or some other unpleasant sensation usually accompanied the increase in venous tone; but the pallor, sweating, and tachycardia that usually accompanied the venous response suggested ganglionic stimulation.

A method<sup>20</sup> for isolating a peripheral venous segment externally for prolonged periods of time by means of a light-weight vein occluder provides an opportunity for testing the effects of smoking upon venous pressure.

2025018414

- 11 -

In a recent follow-up study<sup>12</sup> of almost 1,000 white men in whom the diagnosis of Buerger's disease was made in Armed Forces hospitals from 1942 to 1948, a questionnaire survey of survivors revealed that nonsmokers and those who had discontinued smoking had lower hospital admission rates than persistent smokers. The study did not disclose any significant association between tobacco consumption and amputation rates.

#### Blood Lipids

In numerous (but not all<sup>56</sup>) population surveys,<sup>13,22,28</sup> one finds reports of higher levels of serum cholesterol in smokers than in nonsmokers and a lipoprotein distribution in heavy smokers resembling that in patients with coronary disease; but from such observations it is not possible to determine whether the relationship between smoking and blood lipids or smoking and coronary disease is one of cause and effect. More likely to be of profit are experimental observations focusing on serum lipid concentrations as influenced by smoking or experimental attempts to influence lipid levels by smoking or by the administration of nicotine.

After an intravenous infusion of nicotine, the free fatty acid concentration of the serum of dogs was usually increased.<sup>73</sup> In human subjects who smoked 2 cigarettes over a 10-minute period, the level of serum free fatty acids rose above the presmoking level and was usually still somewhat elevated 20 to 40 minutes after smoking. Essentially no change occurred in the serum cholesterol or triglyceride levels. In subjects who chain smoked 6 cigarettes, the free fatty acid level rose during the 60-minute testing period, in 1 instance as much as 3-fold. These effects on

2025018415

- 12 -

free fatty acids, on other blood lipids, and on fat tolerance are now being followed<sup>73</sup> in both animals and human subjects on a short-term and long-term basis, with emphasis on variations that may be produced by age, sex, smoking habits, and type of cigaret used, in habitual smokers who have stopped smoking and in nonsmokers who have begun to smoke, in normal subjects and in subjects with coronary artery disease. Other phenomena under study include the influence of the sympathetic nervous system and the adrenal glands on the blood lipid response to smoking in normal subjects and in patients who have undergone bilateral adrenalectomy; and the effect of ganglionic blocking agents and of various tranquilizing drugs on the lipid response to smoking.

Noting that subjects show remarkable difference in their blood lipid concentrations on a standard diet and in their blood lipid responses to changes in diet, an investigator<sup>47</sup> believes that a given subject's responsiveness is a function of his cholesterol level on a standard diet and that on this basis one may correct predictions of serum cholesterol levels. He is now applying this concept to a number of factors that may influence serum lipid levels, including the use of tobacco.

#### Pulmonary Function and Disease

What is the relationship between smoking and pulmonary function? Does smoking initiate or promote chronic pulmonary disease-- particularly those common but poorly understood conditions variously called chronic bronchitis and pulmonary emphysema?

2025018416

- 13 -

The answer to such questions might be easy if large groups of healthy young nonsmoking human beings with no detectible disease could be put to smoking over a period of years, controlled for all known interfering factors, and followed by all available diagnostic means. It is unlikely that our society will lend itself to such practices. An alternative that may at least provide leads is to use animals in the same way; or in a way that overcomes their congenital unwillingness to smoke. This is exactly what one grantee<sup>31</sup> has done. Two dogs "smoked" cigarettes through a flap tracheotomy; periodically the dogs were checked by bronchoscopic examination and compared with a nonsmoking tracheotomized dog for mucosal changes in trachea and bronchi. At the time the grant terminated, the dogs had smoked several thousand cigarettes over a period of 1 1/2 years.

Investigators have attempted to determine what percentage of patients with bronchitis or emphysema also smoke cigarettes. No 2 series, however, seem to be strictly comparable, because definitions of smokers and nonsmokers are not the same; and since such variation in smoking habits may exist, it seems impossible to devise comparable but easily tabulated questionnaires to handle large populations. Of 36 patients with chronic bronchitis, 55 per cent had a smoking rate greater than 20 pack years (number of packs per day times number of years smoked), whereas only 15 per cent were in each of the other 3 categories (nonsmokers; less than 10 pack years; 10-19 pack years).<sup>78</sup> In another series,<sup>70</sup> of 80 patients with chronic obstructive emphysema, 69 per cent had smoked 10 or

2025018417

- 14 -

more cigarettes a day, for 10 years or more; the remainder had never smoked.

Current statistics indicate that mortality from all stages of bronchitis in the United States is about 1/30 the British rate. Yet a preliminary study<sup>70</sup> of 100 patients with chronic obstructive emphysema suggested that chronic bronchitis is almost as frequent in this country as in Great Britain. Is chronic bronchitis significantly more frequent, as commonly reported, in smokers than in nonsmokers? The influence of smoking habits upon the onset and course of chronic bronchitis and emphysema will be examined as this analysis is extended to include over 700 patients now being followed. On the other hand, because of the increasing importance of air pollution as a possible etiologic agent in chronic pulmonary disease or as a possible factor in its progression, smoking is sometimes relegated to a minor role, and research<sup>61</sup> formerly supported by the National Heart Institute has been reassigned to the Division of Air Pollution.

Is obstructive emphysema, as some believe, merely a symptom of old age, and would everyone develop it if he lived long enough? Or does it tend to afflict smokers, or those with antecedent pulmonary disease, which may itself depend in part on the patient's smoking history? Is its predilection for men related to male-female distribution of smoking? Why do elderly people with apparently normal cardiopulmonary systems have symptoms that suggest pulmonary insufficiency? This pathogenic web may be partly untangled by

2025018418

- 15 -

a study<sup>65</sup> of respiratory function in a group of about 150 healthy aged men and women over 70 years old; or in a similar study<sup>33</sup> recently transferred to the Bureau of State Services.

The clinical recognition of obstructive pulmonary emphysema still occurs so late in the course of the disease that its origin and progression are not easily traced. Many workers have attempted to devise a technic or an instrument that will permit a diagnosis of incipient respiratory obstruction. Methods for measuring the degree of respiratory obstruction objectively constitute an important means of evaluating the functional abnormalities that may result from inhaling irritating substances, including tobacco smoke. With National Heart Institute support,<sup>55</sup> attempts are under way to redesign the body plethysmograph--a sensitive device for evaluating the patency of the airways and the functional residual capacity, now in use for the past several years--so that it will have better general applicability to large populations in surveys of respiratory obstructive disease; and to develop new plethysmographic methods for determining blood volume, pulmonary circulation time, and other parameters. Elsewhere,<sup>34</sup> the puffmeter--a simple flowmeter shown to be valid and reliable in clinical tests at the Heart Disease Epidemiology program at Framingham--was applied to populations with varying exposures to smoking and to community air pollution. Among the results of these surveys, still undergoing analysis, was the observation that although smoking a single cigaret did not seem to have an effect, cigaret smokers tended to have lower puffmeter test values than nonsmokers. In another

2025018419



- 16 -

attempt<sup>74</sup> to devise a physiologic test of early pulmonary emphysema, examination of pulmonary elasticity in a group of normal nonsmoking young volunteers from Milwaukee colleges will serve as a base line against which the effects of age, smoking, and disease can be evaluated.

Although the physiologic defects in established emphysema continue to receive widespread attention, morphologic definition of the earliest clinically recognizable changes is still largely a virgin field. Seeking an anatomic basis for airway obstruction, an investigator<sup>75</sup> is correlating physiologic changes with pathologic lesions and clinical features with anatomic details. Carefully selected patients are followed in a permanent emphysema registry so that intensive clinical study may antedate autopsy or lung biopsy as closely as possible. Preliminary findings on some 100 lung specimens received so far indicate good correlation between emphysema, pigment deposition, and smoking history. Similarly in a systematic study<sup>78</sup> of factors--including the smoking history--responsible for the development of emphysema, another investigator will examine the widely accepted theory that asthma and chronic bronchitis are precursors. Subjects with chronic bronchitis and normal nonsmoking controls will be followed in parallel over a period of years by clinical, physiologic, and pathologic methods.

Although some reports in the literature indicate that smoking does not affect vital capacity or airway resistance, other methods sometimes reveal changes in pulmonary physiologic tests even in apparently healthy smokers. Such minor degrees of injury may be

2025018420

- 17 -

unrecognized forerunners of incapacitating disease or may at least facilitate its inroads. Heavy smokers--more than 1 pack a day for 18 years--had diminished timed expiratory volume, total lung capacity, maximum breathing capacity, and total and membrane diffusing capacities; and an increased ratio of residual volume to total lung volume.<sup>16</sup> With the body plethysmographic method,<sup>36</sup> after from 10 to 20 inhalations of cigaret smoke, normal subjects, whether smokers or nonsmokers, usually had significant increase in airway resistance for from 10 minutes to an hour, although not enough to cause symptoms or clinically detectible changes. Smoking a cigar without inhalation or merely puffing on a cigaret did not affect resistance. Resistance returned to control values when the subject inhaled a bronchodilator, isopropylarterenol, or did not increase at all if the subject received the bronchodilator before inhaling smoke. In smokers with cardiac or pulmonary disease, whether or not their resistance was increased during the control period, inhalation of cigaret smoke had the same effect as in these normal subjects. Although aerosols of isotonic saline and of nicotine bitartrate did not affect airway resistance, cigaret smoke increased airway resistance to the same degree regardless of whether the nicotine content of the cigaret was high or low. For this and other reasons, the investigators assigned the effects upon airway resistance to the inhalation of a large number of small particles in cigaret smoke.

Attempting to clarify the mechanisms controlling alveolar ventilation and the distribution and volume of pulmonary capillary

2025018421

- 18 -

blood flow, an investigator<sup>38</sup> developed a method of extracting surface-active material from the lungs. The surface tension of this material could be altered by treating it with cigaret smoke or by allowing animals to inhale smoke before they were killed.

#### Neurohormones and Human Behavior

It has long been known that the animal's pressor response to nicotine is at least partly the result of the release of epinephrine by the adrenal glands. Recently, in dogs receiving increasing doses of nicotine sulfate by intravenous administration, the pressor response was found to have a definite relationship to the concentration of epinephrine in peripheral arterial blood, establishing the role of circulating epinephrine in the hypertensive episode.<sup>10</sup> The "massive" concentration of epinephrine appearing in the peripheral circulation--greater than that obtained by any procedure except the intravenous administration of epinephrine itself--was considered an important hypertensive element.

If the sympathomimetic effects--lowered skin temperature, increased pulse rate, metabolic rate, and blood pressure--observed when a person absorbs 3 or 4 mg. of nicotine while smoking a cigaret are produced by the adrenal secretion of epinephrine or norepinephrine or both, the excretion of these catecholamines should also be increased during smoking. This postulation was confirmed<sup>10</sup> in smokers, whose urinary output of epinephrine showed a significant increase--small but consistent--after a 2-hour period of heavy smoking. The output of norepinephrine was insignificant and inconsistent. But the 24-hour excretion of pressor amines was no greater in smokers than in nonsmokers.

2025018422

- 19 -

Working with dogs anesthetized with pentobarbital, an investigator<sup>49</sup> confirmed that nicotine stimulates the adrenal medulla to secrete catecholamines, especially epinephrine, with lesser amounts of norepinephrine. Using an isolated guinea pig heart for measuring epinephrine and norepinephrine in urine, plasma, and tissues--a sensitive bioassay technic that he developed--he is studying the influence of smoking on catecholamines in normal young subjects, correlating the levels with changes in blood pressure.

Injected into dogs, nicotine increased the catecholamine content of the heart.<sup>58</sup> Does this increase represent synthesis within the heart or storage of circulating catecholamines released from the adrenal glands? In an attempt to answer these questions, experiments are in progress in which nicotine is infused intravenously, the heart and adrenal glands are removed immediately after infusion, and the catecholamine content is determined. If the increase in the catecholamine content of the heart is confirmed, an attempt to determine its source will be made by a fractionation method that this group devised.

Tolerance to the repeated administration of nicotine has frequently been reported. Does tolerance arise because the adrenal gland ceases its acute responses to nicotine? In animals chronically "poisoned" with nicotine, an investigator<sup>68</sup> is examining the effect of nicotine tolerance upon the adrenal synthesis and release of catecholamines. Since he had found in earlier experiments that young animals are more likely to become tolerant to nicotine than

2025018423

- 20 -

are older animals, he is comparing the responses of weanling and adult male rats to determine the effects of age. Preliminary results indicate that in an animal that has received chronic treatment with nicotine, the adrenal medulla no longer responds to nicotine administration by releasing catecholamines and no longer responds to nervous stimuli. Does this state of affairs lead to an increased storage of catecholamines?

Although nicotine has an acute stimulating effect upon sympathetic ganglia and adrenal medulla and although smoking usually produces an immediate increase in heart rate, habitual smoking does not seem to affect the basic cardiac neurovegetative status. In healthy American and Austrian men from 17 to 50 years of age, ranging from competitive athletes, mountaineers, and Alpine soldiers to completely sedentary persons, smoking habits--ranging from no smoking to heavy smoking--did not seem to modify the apparent effect of exercise habits on the heart rate.<sup>17</sup> The apparent failure of smoking to produce any permanent effect might be the result either of the "amphotropic" influence of nicotine upon both vagal and sympathetic ganglia or of the relatively brief effects of smoking a single cigaret on cardiac sympathetic tone. But these evanescent effects do not exclude the possibility that the "incessant bombardment" of catecholamines mobilized during habitual smoking may have gradual and cumulative effects upon the heart and circulation.

2025018424

- 21 -

The importance of the hypothalamo-adrenal system in lipid metabolism came under suspicion when rabbits receiving excess lipid in their diet developed a higher blood lipid concentration and more aortic atherosclerosis if they were at the same time subjected to repeated hypothalamic stimulation.<sup>30,59</sup> The suspicion was strengthened by the observation that men with a behavior pattern called "A" and characterized by profound competitiveness and an obsession that time is too short excreted 4 times as much norepinephrine during their working day as did men with a converse behavior pattern called "B." Exposure of a group of accountants to occupational deadlines induced the type A pattern to become manifest in many of them and at such times excited marked increases in serum cholesterol and acceleration of blood coagulation independent of changes in diet, weight, or physical activity. Even though the dietary, drinking, smoking, and exercise habits of type A and type B groups and a third group with a chronic anxiety state were comparable, type A men had much higher serum cholesterol, more rapid blood clotting, higher incidence of arcus senilis, and a much higher incidence of coronary disease than did the men in either of the other 2 groups. When type A and type B women were compared--both groups including a series of nuns, who of course did not smoke--a similar distribution of these features was found; and only women with the type A pattern had a history of myocardial infarction or angina pectoris. Again, the striking differences

2025018425

- 22 -

between type A and type B women were independent of differences in parental incidence of coronary artery disease, caloric or fat intake, obesity, physical activity, smoking, of "femininity." Although persons of type A indulged in more smoking and drinking, these factors appeared to be associative rather than causative in the group's greater tendency to coronary disease.

Smoking produces subtle pleasurable sensations that may be caused as much by a tranquilizing action of nicotine as it is by the physical manipulations of the smoking act. Perhaps it can be demonstrated that smokers and nonsmokers differ in certain personality characteristics that might on the one hand explain their smoking propensity and on the other their tendency to certain diseases. Projective and nonprojective testing and questionnaire methods employed by one investigator<sup>13</sup> already reveal that smokers have a significantly greater tendency to anger and urge to eat under stress and that nonsmokers more often show diminished activity under stress and give a higher number of white space responses in the Rorschach test. In other Rorschach items, however, no significant differences could be determined in productivity, construction, proportion of the whole, detailed and very detailed responses, or distribution of color responses. Tests of figure drawing are undergoing analysis.

2025018426

- 23 -

The fact that heavy smokers were found to consume more meat and eggs and less fat in the form of cakes, sweets, and chocolates than nonsmokers suggested to one group of investigators<sup>28</sup> that smoking might affect food preferences through taste mechanisms. In 2 separate samples--young medical students about 20 years of age and older insurance personnel about 28 years of age--smokers and nonsmokers manifested no significant differences in taste thresholds with respect to salt, sour, and sweet; but cigaret smokers had a significantly higher taste threshold for quinine than nonsmokers and showed a progressive deterioration with age in their sensitivity for bitter. Since the inability to taste bitter might be genetically transmitted, tests with phenylthio-carbamide (PTC) were performed but failed to reveal any difference between smokers and nonsmokers, suggesting that the decrease in sensitivity to bitter is the result of addiction rather than genetic in origin and that perhaps the alkaloids in tobacco smoke fatigue the mechanisms for perception of bitter. (But others<sup>13</sup> report significantly more PTC tasters among heavy smokers than among nonsmokers; see p. 43).

#### The Fetus

It is now accepted that women who smoke during pregnancy may show some increase in the carbon monoxide content of their blood, and it has been suggested that smoking during pregnancy may possibly influence the weight of the newborn or induce fetal death, prematurity,

2025018427



- 24 -

or maldevelopment. May smoking also have an effect upon the fetal circulation? And can such an effect be detected during pregnancy so that the unfavorable fetal environment may be altered?

Although nicotine is usually believed to affect the heart only through the intermediary of nervous elements, it may have a direct action upon the preneural embryonic myocardium. The preneural rat heart stimulated with increasing doses of nicotine underwent progressive slowing of the spontaneous contraction rate: from 13 per cent deceleration at 50 mg./L. of nicotine to 56 per cent at 400 mg./L.<sup>9</sup> Usually the amplitude of contraction diminished, and irregularity and incoordination were frequent. Studies of the mechanism of these effects are in progress.

Employing fetal phonocardiographic equipment developed under grant support, an investigator<sup>32</sup> is able to record long-term experiments with loss of less than 1 per cent of data and to establish patterns of fetal heart rates during the course of pregnancy and labor. Experiments devised to insult mother and fetus have as their objectives a better understanding of mechanisms protecting the fetus from maternal stresses and the detection of incipient fetal cardiac abnormalities. With such devices, both cigaret smoking and nicotine provide satisfactory maternal stimuli. A number of smoking experiments on normal gravida have been carried out.<sup>32</sup>

The effect of maternal cigaret smoking upon the fetal heart rate and the character of the fetal electrocardiographic complex captured the attention of other researchers.<sup>14,71</sup> A new type of vaginal electrode makes it possible to record the fetal electro-

2025018428

- 25 -

cardiogram throughout labor and delivery without electrical "noise" and without restraining the mother.<sup>71</sup>

Ballistocardiography and Electrocardiography

Little<sup>23</sup> or no<sup>1</sup> ballistic change occurred in normal young habitual smokers after smoking either commercial "low nicotine" cigarettes or their accustomed brand<sup>1</sup> or after receiving nicotine by intravenous injection.<sup>23</sup> An increase in pulse rate and decrease in skin temperature were interpreted as the result of constriction of peripheral vessels.<sup>1</sup>

Absent in high school boys and therefore probably not an indication of susceptibility to tobacco,<sup>6</sup> temporary deterioration of the ballistocardiogram on smoking a standard cigaret was common, in coronary artery disease and in the elderly, and could be observed in apparently normal adults.<sup>3,6</sup> These ballistocardiographic phenomena could not be explained by the fact that tobacco constricts peripheral vessels, increases the diastolic blood pressure, and accelerates the heart because their occurrence was independent of the latter effects. Smoking a single cigaret may so distort the ballistic record as to suggest the incoordination of cardiac contraction observed during a spontaneous attack of angina pectoris.

The cigaret test produced ballistic deterioration in 7.5 per cent of normal subjects and almost 50 per cent of patients with clinical coronary artery disease, without respect to previous smoking habits, smoke inhalation, or the presence of angina pectoris or "remote" myocardial infarction.<sup>2</sup> Although neither denicotinization or various types of filters prevented these ballistic

2025018429

- 26 -

alterations, sublingual administration of nicotine produced similar deterioration, and nicotine was considered the causative agent. Since all the subjects were men and half of them were more than 60 years of age, the deteriorated ballistic response in "normal" subjects might actually have been an indication of coronary atherosclerosis. Although patients more than 50 years old frequently have abnormal resting ballistic tracings or the tracing becomes positive upon smoking, the test seemed a valuable stress procedure in subjects below that age.

Systemic injection of either nicotine or its synthetic congener, I-I-dimethyl-4-phenylpiperazinium iodide, gave the same biphasic response in dogs: the initial systemic pressor effect and decreased amplitude of the ballistic systolic complexes were succeeded by signs of cardiac stimulation and an increase in the amplitude of the record to well beyond control levels.<sup>3</sup> A lighted cigaret inserted into the air intake of the respiratory pump produced the same biphasic effect, although more gradual in onset and of longer duration. Ballistic improvement was also elicited by intracoronary injection of either nicotine or its congener several hours after the circulatory shock of acute myocardial infarction. These results suggested that the clinical ballistocardiographic smoking test, which uses nicotine as a circulatory stressor agent, can be wrongly interpreted if inaccurate timing causes the initial effect of hypertension without cardiac stimulation to be missed, the later

2025018430

- 27 -

phase of cardiac stimulation suggesting negative results, that is, an unimpaired heart; and that revision of clinical criteria for interpreting the test might improve its diagnostic validity.

Although the ballistocardiographic cigaret test separates patients from controls more frequently than the ballistocardiogram itself, smoking is said<sup>2</sup> to produce minimal electrocardiographic effects. In a large carefully screened sample of healthy subjects an analysis of the effects of smoking upon the electrocardiogram is included in an ongoing study<sup>64</sup> of electrocardiographic characteristics as related to constitutional factors and physiologic stresses.

#### Carbon Monoxide

Although carbon monoxide represents about 4 per cent of the gas phase of tobacco smoke and exposure to a 1 per cent concentration of carbon monoxide is lethal for human beings within 1/2 hour, tobacco smokers do not suffer from recognizable carbon monoxide poisoning. Even 30 per cent saturation of the blood with carbon monoxide usually produces no symptoms, although some believe that a saturation of 10 per cent significantly affects oxygen transport and may be especially hazardous in persons particularly vulnerable because of incompetent heart, lungs, or hemopoietic systems. Blood levels of carboxyhemoglobin are said to be about 2 per cent or less in nonsmokers and as high as 5 per cent in most smokers. Under research grant support,<sup>7</sup> results of some 200 determinations

2025018431

- 28 -

of blood carbon monoxide levels indicated that as much as 12 per cent of the oxygen-carrying capacity might be displaced by carboxyhemoglobin in heavy smokers without lung disease. The low concentration that usually prevails in human subjects, however, probably results from intermittent exposure during the act of smoking and from dilution of the smoke in the lungs.

Smokers tend to have a lower pulmonary diffusion of carbon monoxide than do nonsmokers and their average carboxyhemoglobin saturation is 4 times higher (4%) than is that of nonsmokers (1%).<sup>16</sup> With a method that they developed for determining blood and alveolar carbon monoxide levels, investigators<sup>70</sup> are attempting to discover whether carboxyhemoglobin saturation is indeed a reliable index of smoking habits. Comparing smokers who inhale with those who do not, they are examining the effect of filters, variations in the smoking habits of men and women, and the relation between smoking and such factors as stress and the time of day.

2025018432

## OBSERVATION OF POPULATION GROUPS

Epidemiology can no longer exist without the help of a host of other disciplines that include physiology, pathology, biochemistry, and biophysics. The epidemiologic approach begins, however, with observation and proceeds with experiment only when this appears a necessary maneuver to clarify observed events. As far as conclusions about smoking are concerned, epidemiologic surveys might be more productive if the populations they examine could be combined to yield vastly larger groups with greater possibility for categoric breakdowns.

In many population studies supported by the National Heart Institute, smoking is a fact of life that must be considered. But it is one of many other facts of life that may contribute to the occurrence of heart disease, perhaps only at some particular stage or when associated with other elements. Its role may have been so subordinate at the time a protocol is written that it is not even mentioned among the elements to be documented; or perhaps it is mentioned in so passing a manner that it is ignored by the indexer. Indeed, it is difficult to see how an epidemiologic dietary study can reach generally acceptable conclusions unless the smoking factor is taken into account. Thus, although a number of projects that include an inquiry into smoking habits are described in the following pages, others now under way probably

- 30 -

assume that a tobacco questionnaire is too minor and too routine to mention in the presentation of plans even though it may be contained in their operative procedure.

But the very fact that smoking does not have a prominent place in population surveys means that the question of its hazards will probably not be answered even in the most comprehensive studies described here. The lack of uniformity in questionnaires, the many overlooked or disregarded variations in smoking habits, and too many other possible influential factors will tend to befog the smoking issue.

#### RETROSPECTIVE APPROACH

In the usual retrospective approach the autopsy reveals arterial lesions and the family then undergoes a structured interview for information about the deceased person's smoking habits, physical activity, alcoholic consumption, dietary habits, and other pertinent facts. One advantage of such an approach is that clinical disease no longer becomes the demarcating point between the positives and negatives in the total study, and even minimal (that is, preclinical) lesions--which may have stronger or weaker associations with suspected causes than do clinical ones--as detectable by currently available pathologic methods, may be examined.

Thus, in consecutive autopsies on patients from 10 to 69 years of age, one group<sup>77</sup> classified the pathologic lesions of atherosclerosis as fatty streaks, fibrous plaques, complicated lesions, and calcifications. When such lesions are examined in all

2025018434

- 31 -

autopsies, including accidental deaths, the contribution of the suspected causative factor may be quite different from what it is when only clinically recognizable involvement is considered. When this procedure, as part of the collaborative Interamerican Atherosclerosis Study, is pursued in a total of 18 laboratories around the world, including Central and South America, the Caribbean, Africa, Europe, and the far East, with the dissected specimens from coronary and cerebral arteries and aorta and the background information sent to a central laboratory, arterial lesions in widely differing populations may be assessed in a uniform manner; and the contribution of smoking as compared with other possible factors may be defined.

Other investigators<sup>4,41</sup> determining the amount of atherosclerosis present at autopsy and its relationship to ischemic heart disease are attempting to relate the pathologic findings to the histories-- including the smoking pattern--subsequently obtained from family informants. Noting a close association between the degree of a given subject's aortic sclerosis and his generalized arteriosclerosis, an investigator<sup>4</sup> found that about 1 in 8 persons had less than average aortic sclerosis and 1 in 8 had more than average. Presumably he is trying to ascertain whether the former were non-smokers, the latter heavy smokers. Unfortunately, the degree of coronary and of aortic sclerosis did not coincide; and myocardial infarction occurred almost as often in men with a scant amount of

2025018435



- 32 -

aortic sclerosis as in those with an average amount. Perhaps those with the scant amount who still develop coronary disease are the smokers--another line of investigation. But in groups with severe aortic sclerosis (at least 15 years more severe than in average age standards) the incidence of myocardial infarction was 5 1/2 times as great as in groups with sclerosis at least 15 years less severe than standard. The antecedents of urban Bantu dying of coronary disease are the source of similar information for correlation with postmortem findings.<sup>45</sup> In an ongoing study in Israel,<sup>48</sup> a psychosocial questionnaire administered to the nearest relative of carefully autopsied subjects seems to reveal a positive correlation between cigaret smoking and ischemic heart disease.

Perhaps many new facets can still be examined in carefully conducted necropsies. In a large number of cases of sudden death from coronary occlusion, phagocytes containing brown pigment were observed<sup>5</sup> within alveoli and sometimes within their walls. Although they resembled heart failure cells, their pigment did not stain for iron, nor was there other evidence of heart failure. When the presence or absence of these cells was correlated with the smoking history obtained from the families of 35 of the autopsied patients, it was discovered that the phagocytes were absent in all the nonsmokers and present in large numbers in the lungs of almost every one who had smoked 1 or more packs a day. In a single exception, it was assumed that the smoker did not inhale.

2025018436

- 33 -

#### PROSPECTIVE APPROACH

A disadvantage of the retrospective method is that the history of the lesion of interest is taken after the person most concerned is no longer available. It must be presumed that the next of kin has sufficient motivation and knowledge to supply the wanted information. Presumably the prospective study can overcome this disadvantage. But the prospective study must be large enough to include during its pursuit sufficient deaths from the lesion under examination. And the prospective study must last long enough and must start with young enough patients to observe the influence of agents that may be acting over a period of many years.

#### Cooperative Studies

A cooperative study of the epidemiology of heart disease is attempting to include these necessary features. In a series of small towns and villages affording contrasts in the mode of life among stable populations, in the frequency of heart disease, and in the relative amounts of dietary fat, large groups of men from 40 to 59 years of age are the subjects of a series of long-term studies conducted in the United States;<sup>51</sup> in 2 farming sections contrasting in their reported frequency of arteriosclerotic heart disease in Finland,<sup>52</sup> which has a higher cardiovascular mortality than other European countries; in 2 rural areas in Yugoslavia,<sup>53</sup> in 1 of which coronary disease seems to be increasing; in 3 large villages together with their environs in Italy,<sup>50</sup> all with moderate fat diets low in saturated fats; in 2 series of villages in Greece,<sup>76</sup> both with diets low in saturated fats but one of which has a more

2025018437

- 34 -

western and sophisticated mode of life than the other; and in a small town in the Netherlands,<sup>62</sup> where the diet is rather high in fats, including saturated fats, and where mortality from severe atherosclerosis and its sequels is increasing. All these investigations have the same research plan and operate according to methods outlined by a central organization, which also provides for exchange of experts, chemical analyses, and data processing. The smoking habits of these subjects are under consideration, along with their dietary habits, medical history, clinical diseases, physical examination, and emphasis on items of special concern.

From the efforts of this group of workers interesting observations have already issued:

In the United States,<sup>56</sup> a prospective study was begun in 1947 on about 300 middle-aged business and professional men and a smaller number of young men 20 to 30 years of age; some 300 men from these original groups are now undergoing periodic reexaminations. Comparison of smokers, nonsmokers, and former smokers is an important element in the survey of aging trends in relation to occupation, economic status, and biologic characteristics. In an analysis of these men, although smokers seemed to have a faster heart rate than nonsmokers, they gave no evidence of reduced circulatory "fitness." The blood pressure of heavy smokers was not significantly lower than that of nonsmokers of the same age if their lower body weight was taken into consideration. Men who voluntarily stopped smoking

2025018438

- 35 -

for 2 years tended to put on an average of 10 pounds in weight, perhaps because smoking inhibits hunger contractions. (But others<sup>13</sup> found a greater proportion of heavy subjects among smokers.) Although others<sup>13,22,28</sup> noted significantly higher cholesterol levels in smokers, smoking patterns showed no relationship to serum cholesterol. Smokers had the same total lung capacity as nonsmokers but a smaller vital capacity and a greater ratio of residual volume to total lung capacity, suggesting that smoking is indeed a factor in increasing airway resistance.

In some 800 men in Finland,<sup>52</sup> heavy smoking was somewhat more predominant among the lumberjacks, who constituted almost one half of the group under study. Both groups had the same cholesterol level. Yet lumberjacks had significantly fewer electrocardiographic changes indicative of past coronary infarction or myocardial ischemia than other men of the same age. Selection and the protective action of exercise were suggested to explain these occupational electrocardiographic differences.

#### Ethnic and Migratory Influences

Complementing this body of work on the epidemiology of heart disease but not an integral part of it, surveys of race, diet, and the mode of living as factors in atherosclerosis are in progress in other countries. In Chile,<sup>46</sup> because a preliminary survey indicated that atherosclerosis was more than 2 1/2 times as common among white farm workers as among Araucanian Indians with similar dietary habits living in reservations and engaged in

2025018439

- 36 -

agricultural work, larger population samples are now being followed in an attempt to determine whether the difference is truly racial and whether it disappears when the diet and the way of life change under urban influence. Again, tobacco consumption is included among the personal habits under consideration. Hawaii, said to offer a "unique laboratory" for medical research among contrasting ethnic and racial groups living together "harmoniously" in the same setting, "without wide social and economic chasms," is the site of an ethnic cardiovascular survey<sup>66</sup> in which information on social, ethnic, occupational, and related habits--including smoking--is obtained by an interviewer able to speak the Hawaiian tongue. In Israel, an investigator<sup>48</sup> is attempting to relate coronary disease to the diet and mode of life in a series of studies. More than 2,000 seminomadic Bedouin--among whom myocardial infarction is said to be rare--Arab villagers, and mostly Jewish port workers were subjected to medical, electrocardiographic, biochemical, and nutritional studies and to a psychosocial questionnaire. The latter, designed to test certain facets of a hypothesis that 3 factors--personality, environmental stress, and the manner in which persons react to the stress--predispose them to myocardial infarction, included information on smoking habits.

The observation that hypertension seems to have a higher prevalence<sup>37,67</sup> among Negroes than among Caucasians in the United States, the West Indies, the Bahamas, and portions of Africa and that coronary disease shows a decreasing prevalence<sup>28</sup> in European,

2025018440

- 37 -

Cape Colored, and Bantu has spurred investigators to determine the cause of apparent racial differences and the role of smoking. In South Africa,<sup>28</sup> in men 40 to 55 years of age, the differences in coronary disease prevalence corresponded with differences in the mean racial serum total cholesterol levels and with differences in the fat content of the diet. In each race, as well as age group and economic class, the alpha-beta lipoprotein distribution in heavy smokers was similar to that in patients with ischemic heart disease. In another South African study,<sup>45</sup> comparisons are being made between rural Bantu populations, whose mortality from coronary artery disease is low; urban Bantu, who seem to die from coronary occlusion at a rate similar to that of the corresponding age group (45-64 years) in Italy; and long-term white prisoners, who seem to conform to the Bantu prisoners and to rural Bantu in diet, metabolism, health status, and low death rate from coronary disease.

To supplement studies supported by the National Heart Institute in non-Caucasian populations living under primitive conditions or in isolated island groups, a survey<sup>67</sup> of white and nonwhite populations in White Plains, New York, is in progress to determine whether hypertension predominates in either group and whether racial differences or other etiologic factors, such as smoking habits, are at fault. In a random sample of more than 2,000 subjects over 35 years of age selected from the total population of Charleston County, South Carolina, which is almost 50 per cent negro, the striking predominance of cerebrovascular deaths and hypertensive

2025018441

- 38 -

cardiorenal disease in Negroes and of coronary thrombosis in white persons is under study.<sup>37</sup> In Evans County, Georgia, where the white:negro distribution is about 3:2, professional experience over a decade has suggested that here, too, Negroes are less susceptible to coronary disease and more subject to hypertension.<sup>29</sup> The validity of the former observation and its relationship to a number of possibly related parameters, including the use of tobacco, are under examination.

Major differences between mortality rates in the United States and the United Kingdom--particularly a higher U.S. rate for coronary artery disease and a higher U.K. rate for bronchitis, pneumonia, and lung cancer--aroused a British investigator's<sup>54</sup> desire to determine whether the discrepancy is real, the result perhaps of smoking habits or degrees of air pollution, or whether divergent diagnostic criteria can explain them. Field studies in both countries were designed to permit useful comparisons between the respective diagnostic practices. Besides the comparisons between British immigrants to the United States and native-born residents of Great Britain and of this country, Norwegian immigrants living in the United States and native-born residents of Norway--a country with a low mortality from both chronic respiratory and cardiovascular disease--are included in order to evaluate the possible selective effect of migration. If differences between mortality rates in the 3 countries are truly environmental, the "American effect" should increase with increasing residence in the United States.

2025018442

- 39 -

Community and Socioeconomic Influences

In contrast to this interest in racial and migratory effects, the "human population laboratory" enclosed in the walls of its own community may serve as the test body in which smoking is included as one of the potential etiologic factors in the genesis of heart disease. Seeking to disentangle general, physical, and intrinsic biologic factors from the maze of disease-producing influences by means of long-term observations, an investigator in a National Heart Institute-supported<sup>72</sup> facility in Alameda County, California, is attempting to develop concepts of disease causations more inclusive than the usual biologic, physical, and chemical influences. Among the projects of this group is the intent to distinguish the possible tension effects of cigaret smoking from the physicochemical effects.

Populations defined by occupation, by socioeconomic group, or by membership in health units also form the nucleus of longitudinal surveys in which tobacco habits constitute one of the many personal characteristics that must be weighed as a part of the mode of living. The rate at which clinical coronary disease develops in such groups is the usual focus. Among populations included in such surveys are a study group of 700 persons with various cardiovascular diagnoses whose work experience was compared with that of an equal number of control persons;<sup>15</sup> some 10,000 white male members of a Jewish fraternal organization;<sup>22</sup> employees

2025018443



- 40 -

in both sedentary and physically active occupations with 10 or more years of service on major northwest railroads;<sup>24</sup> more than 2,000 employees of the Western Electric Company in Illinois;<sup>25</sup> 1,200 Benedictine and 600 Trappist monks, whose diets can be carefully monitored, the former on a daily 2,900-calorie relatively high-fat, the latter on a 3,200-calorie relatively low-fat diet;<sup>27</sup> male civil service employees in Albany, New York;<sup>27</sup> occupational groups in a North Dakota city;<sup>27</sup> over 1,800 Los Angeles men in categorized occupational groups ranging from professional through skilled worker to laborer-custodial;<sup>39</sup> industrial workers in Chicago;<sup>44</sup> and some 110,000 persons enrolled in the Health Insurance Plan of Greater New York.<sup>69</sup> These surveys will provide a large number of observations on essentially heterogeneous populations, often at the earliest possible moment of their clinical disease. But the weakness in all such studies of coronary artery disease is that even when they include examination of persons without characteristic complaints, they cannot detect, during the life of the subject, coronary sclerosis that does not produce symptomatic or electrocardiographic manifestations. Included in one of these surveys<sup>44</sup> is a program for evaluating possible preventive measures in coronary disease. Guided correction of what is believed may be lower risk levels of habits of eating, physical activity, and smoking seems to be producing in high-risk middle-aged male volunteers improved scores in cardiopulmonary fitness tests and in the incidence of clinical coronary disease.

2025018444

- 41 -

From such epidemiologic efforts, little can be expected beyond a delineation of the relationship between smoking habits and the frequency of heart disease. Thus, among men of Jewish origin, under 51 years of age, although no distinctions could be drawn when the daily consumption of 20 cigarettes was taken as the dividing line, coronary disease was present in about 12 per cent of 179 "heavy smokers" (more than 40 cigarettes a day) and in only 6.5 per cent of the other 1,521, who smoked less than 40 cigarettes or none at all.<sup>22</sup> For heavy smokers, the ratio of myocardial infarction to isolated angina pectoris was 1.3:1; for other categories it was 0.5:1. The serum cholesterol was also higher in heavy smokers. These statistical associations were not assumed to indicate causal relationships between smoking and coronary disease because smoking also seems to be associated with other potential atherogenic factors, such as endomorphy and mesomorphy and consumption of saturated animal fats; but the ratio of clinical myocardial infarction to isolated angina pectoris suggested that heavy smoking may precipitate an acute episode when coronary artery disease is already present--hardly a novel concept!

#### Genetic Influences

Do coronary artery disease and hypertension "run in families"? Or more learnedly, is there a familial diathesis to these diseases? And if so, how does smoking influence the picture? Genetic influences in coronary artery disease and hypertension will probably continue to intrigue investigators for a long time--or at

2025018445

- 42 -

least until the answers to many questions are found.

In the town of Tecumseh, Michigan, with a population of about 8,300 belonging to 3,400 bloodlines, all subjects with recognizable cardiovascular disease, including hypertension and such related conditions as diabetes, are being followed and analyzed according to kindreds to detect familial aggregations of heart ailments.<sup>42</sup> For all patients with myocardial infarction hospitalized in Hartford County between 1940 and 1949 and all those hospitalized for this condition during the tenure of the grant,<sup>57</sup> the siblings and offspring are sought out and followed by physical examination for the presence or onset of coronary disease. Similarly, the family of patients dying of myocardial infarction or surviving the episode are the subjects of another genetic study<sup>43</sup> in Baltimore. Because a pilot survey indicated that Irish living in Boston have a higher serum cholesterol and a greater incidence of hypertension, but a smaller content of animal fat in their diet, than do their brothers living in Ireland, an investigator<sup>79</sup> hopes to compare 500 pairs of brothers in the 2 areas to evaluate the relative contribution of genetic and nutritional influences to cardiovascular disease, particularly coronary disease. The relative importance of heredity and environment in the pathogenesis of primary hypertension is also commanding attention in New York City,<sup>35</sup> where the relatives of hypertensives will be compared with those of nonhypertensives and the earliest onset of the disease detected in double hypertensive offspring less than 40 years of age, reexamined over a period of years; and in Buffalo,<sup>40</sup> where

2025018446

- 43 -

blood relatives of hypertensive subjects are being compared with nonblood relatives living in the same household. In all such studies smoking habits are examined; but a smoking history of subjects already dead at the onset of the investigator's query must be obtained from the survivors.

On a smaller scale but with a longer duration than most epidemiologic surveys, genetic influences are a prime concern in a long-term study<sup>13</sup> of the precursors of hypertension and coronary artery disease in about 1,000 medical students in 16 consecutive classes receiving periodic follow-up examinations after graduation. When the effects of smoking a single cigaret were studied by ballistocardiography, the differences between the offspring of hypertensive or coronary parents and those of "normal" parents suggested that the circulatory response of healthy young adults to smoking depends at least in part on their heritage: those with hypertensive parents displayed an exaggerated increase in cardiac output and rise in systolic and diastolic blood pressure; those with coronary parents had a more marked decrease in stroke volume, resulting in a smaller increase in cardiac output. About 60 per cent of students graded highly susceptible to hypertension and coronary disease by parental history and individual characteristics were smokers; the same proportion of those graded least susceptible were nonsmokers; 2 groups with intermediate susceptibility had equal numbers of smokers and nonsmokers. The fact that heavy cigaret smokers showed a strikingly higher proportion of phenylthiocarbamide (PTC) tasters than nonsmokers suggested a genetic difference between

2025018447

- 44 -

the 2 groups. (But others<sup>28</sup> have found no difference in the distribution of PTC tasters among smoker and nonsmoker samples; see p. 23).

2025018448

## EPILOG

Certain facts may emerge from the research described in the preceding pages: When compared with nonsmokers, smokers exhibit higher serum cholesterol levels; a greater tendency to anger, greater urge to eat, and greater activity under stress; a poorer showing in tests of pulmonary function; a higher urinary output of epinephrine; and a few other disjointed characteristics. But a pair of questions may rear their interrogation points for a long time: For some of these observations, is smoking the cause, the effect, or merely incidental? For others, though smoking now seems to be the cause, how enduring is the effect?

As far as the population surveys are concerned, it is apparent that smoking has been relegated to a relatively minor role. Obviously no single study is large enough to do more than indicate trends; and how can the trends be combined when the methods of sampling and the approach--in this case, the smoking questionnaire--vary so from one study to another and are never really comparable? Can all smoking categories be separated or even distinguished--not only the number of cigarettes (or cigars or pipes of tobacco) smoked each day, but the length that is really smoked as compared with the length that burns unheeded on the desk top, the amount of denicotinization of the cigaret, the simultaneous inhalation of

- 46 -

other beneficial or noxious agents, not to speak of the age at onset of smoking, the nonsmoking intervals, and a host of other factors? Where draw the line between smoking and nonsmoking? Are 5 cigarettes a day in the smoking or nonsmoking category? To choose a single possible source of error, a person who smokes 2 packs of cigarettes a day may actually be taking only the initial puff that lights each one, letting the rest of the cigarette burn itself out. But a man who smokes only a few a day--less than half a pack perhaps--may smoke them all from the first puff to the bitter end, almost continuously. The first man is classed as a "heavy" smoker, the second as (virtually) a nonsmoker, and the correlation is built up on such misconstructions. How easy it would be to miss differences because smoking habits are not sharply definable or defined and to assume differences that only appear to exist.

The complex physiologic actions of nicotine (and perhaps of the large number of other components in tobacco smoke) render interpretations extremely difficult. The known circulatory effects seem to be acute or transient rather than chronic, the known pulmonary effects mainly nonspecific, the result of particle inhalation. The carcinogenic and cardiovascular effects of smoking have been divorced in the minds and work of most investigators; but should they be? More animals, particularly primates, could be--and should be--"taught" to "smoke" and observed simultaneously for carcinogenic and cardiovascular effects over their lifetime. This may not give the human answer, but it might suggest some important leads concerning chronicity in rigidly controlled smokers.

Chronic effects can be judged only with time, and for human beings the time is long. Large groups of people must be allowed

2025018450

- 47 -

to smoke or to forgo smoking--as they choose, after subtle indoctrination--over a period of years, their diet and a vast number of other possible etiologic factors (including poorly understood social and psychologic variables) strictly controlled. And since smoking may merely be reinforcing other causative agents (air pollutants? diet? stress and strain?) that might not be active in particular groups under observation, a survey that revealed no effects from smoking might be meaningless. It should be possible to build surveys about large conglomerations of people who do not smoke, perhaps because of religious tenets, or whose smoking habits could be rigidly observed. The tendency to heart disease in a number of such conglomerations has already received attention, but have the smoking histories of the persons comprising these groups been sufficiently analyzed? Such observations cannot be made overnight; but it might be possible to review completed dietary studies of such conglomerations from the point of view of smoking patterns.

Specialization may already have reached the point of least return. Carcinogenic agents contained in smoke will produce cancers when administered under the proper circumstances to the proper animal species; how much further can this aspect be pursued? Perhaps the moment has arrived for overcoming the difficulties of working with whole tobacco smoke and for observing its carcinogenic and cardiopulmonary effects together over prolonged periods. Perhaps carcinogenic studies of smoking components could be combined with

2025018451



- 48 -

cardiovascular studies, with profit to both. Perhaps the collaborative approach applied to the large number of ongoing epidemiologic surveys would permit smoking questionnaires to be standardized and expanded and would at least give equal emphasis to smoking habits and dietary patterns. Needless to say, such collaborative expansion entails an intensified research effort--and a lot of time.

2025018452

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2025018454

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2025018455

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2025018457

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2025018458

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73. H-5989 Alfred Kershbaum and Samuel Bellét; Philadelphia General Hospital, Philadelphia, Pennsylvania. Smoking and nicotine effects on blood lipids.
74. H-6004 William W. Stead and Thomas R. Simon; Marquette University, Milwaukee, Wisconsin. Development of improved test of pulmonary ventilatory function.
75. H-6067 Roger S. Mitchell and Giles F. Filley; University of Colorado, Denver, Colorado. Correlation of physiology and pathology in emphysema.
76. H-6090 Christ Aravanis, Demetrios Lekos, and A. S. Dontas; University of Athens, Athens, Greece. Cardiovascular epidemiology in Greece.
77. H-6581 Henry C. McGill, Jr.; Louisiana State University, Baton Rouge, Louisiana. Natural and experimental atherosclerosis.
78. H-6751 Attilio D. Renzetti, Jr.; University of Utah, Salt Lake City, Utah. Physio-pathologic study of chronic bronchitis.
79. H-6892 Fredrick J. Stare, D. M. Hegsted, M. F. Trulson, and W. E. J. Jessop; Harvard Medical School, Boston, Massachusetts. Nutrition and cardiovascular disease in siblings and racial groups.

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COMPELLED PRODUCTION

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B. OCCUPATIONAL EXPOSURE

Many workers exposed to various dusts, tars, oils, etc., in certain specific industries have developed lung cancer. The absolute numbers of these persons is relatively small, but as Kotin and Hueper (786-A) have pointed out, the effect of these various substances may be more widespread than is generally realized in that persons living in the environment of plants producing such injurious substances may be exposed although to a lesser degree than the persons working in the suspected establishment.

Cornfield et al. (3409) disagreed with Kotin and Hueper (786-A), pointing out that the population exposed to occupational carcinogens is small, hence these agents cannot account for the increasing lung-cancer risk in the remainder of the population.

V-B-1

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# 1. Inorganic Chemicals

## a. Nickel

Exposure to nickel fumes, dust of metallic nickel and its compounds, or to nickel carbonyl vapors, is frequent for industrial workers of many types and in many operations. Skin contact with nickel and nickel salts often results in an allergic dermatitis. Inhalation of nickel carbonyls has resulted in an appreciable number of acute and often fatal poisonings. Various pulmonary manifestations are apparently attributable to the toxicity of finely dispersed nickel formed by nickel carbonyl decomposition in the lungs.

Lung cancer in nickel workers was first noticed in 1924 by Baader (1471). From 1924 to 1948, 82 cases of lung cancer, no cases of laryngeal cancer, and 47 cases of cancer of the nose were reported. Experimental substantiation of the carcinogenic activity of nickel has been provided by Campbell (1537), who exposed mice to powdered nickel matte and observed a significantly higher pulmonary tumor incidence in the test animals than in the controls. Also, Hueper produced tumors at the site of application in 50 of 175 rats by implantation of nickel powder. Nickel has been observed in lung tissue of exposed persons in amounts ranging from 0.2 to 6.3 mg./kg. of lung tissue.

Hueper (970-B) has concluded that the respiratory carcinomas observed among nickel workers are due to more or less finely dispersed nickel particles or vapors.

b. Chromium

Metallic chromium, alone or alloyed, and chromium compounds are used extensively in industry. Hueper (970-B, 2807-A) has listed several scores of occupations in which the workers are exposed in varying degrees to chromium and/or its compounds.

Mancuso and Hueper (281) suspect that the carcinogenic activity of chromium and/or its compounds is a property possessed by the insoluble or slightly soluble forms, since these insoluble types would more readily be deposited and retained in the lung. A high concentration of chromium has been found in the lungs of exposed workers and also in the blood. Animal experimentation indicates that inhaled chromite ore is solubilized in the rats' lung with a concomitant rise in the blood chromium level (1158-A).

American observations indicate a frequency of lung cancer in chromate workers 13 to 31 times the normal frequency observed in the general male population. In German chrome pigment workers, over 50 percent of the lung cancer cases were men under 40 years of age, when lung cancer is relatively infrequent.

Gross and Koelsch (1666-A) and Campbell (1537) were unsuccessful in their animal experiments with chromate dust but Schinz and Vollmann produced one lung tumor in a rabbit by implantation.

The total number of recorded cases of lung cancer attributable to exposure to chromate was reported by Hueper (970-B) in 1956 to be around 125.

c. Arsenic

Excessive lung cancer incidence has been reported in workers exposed to various arsenicals. Prolonged inhalation of arsenical dust and fumes appears to produce an increased liability to cancer of the lung. With respect to the total evidence incriminating arsenic, Hueper (970-B) stated in 1956:

"However, the existence of such connections should be acknowledged only when there existed at some time clinical and, if possible, histological and biochemical evidence of chronic arsenicism. In view of the absence of any such evidence associated with chronic arsenicism among the nickel refinery workers affected by cancers of the nasal cavity, paranasal sinuses, and lung, and among excessive tobacco smokers with cancer of the larynx and lung, it is most unlikely that exposure to arsenic dust, fumes, and vapors plays any role in the production of respiratory cancers in members of these population groups."

V-B-4

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d. Iron

As a result of the extensive production and use of various types of iron and its products, many workers are exposed through inhalation of dust and fumes of iron, iron alloys, and compounds. Kennaway et al., Turner and Grau, and Campbell, among others, have reported an excessive lung cancer incidence among iron workers. Animal experimentation has yielded equivocal results; exposure to iron oxide and hematite produced no lung tumors in rats and guinea pigs in one study, and a higher incidence of lung tumors in mice so exposed in another study (1537).

According to Huser (970-B), critical evaluation of the available evidence in respect of iron as an occupational carcinogen indicates that

"...it is still uncertain whether an exposure to iron dust conveys an abnormal liability to lung cancer."

and

"...thorough and comprehensive epidemiological data on the incidence of lung cancer in workers exposed to iron dust are not available. Hence, a definite conclusion on this problem must be withheld."

V-B-5

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e. Beryllium

Since 1920, beryllium and/or its compounds has found significant industrial usage. Workers exposed to these have manifested various respiratory disfunctions of both a chronic and an acute nature. Beryllium is retained both in human and mammalian lungs (as well as in the bones, where it replaces calcium) for extended periods after exposure. Exposed workers, as well as some persons living in the immediate neighborhood, develop berylliosis.

Hueper, in 1948, suggested that berylliosis may be followed by malignant lesions, a proposal received skeptically by other investigators.

Animal experimentation has yielded osteogenic sarcomas in rabbits after beryllium oxide inhalation and bronchogenic carcinomas in rats inhaling both soluble and insoluble beryllium compounds. Kahlau (730), in support of Hueper's contention, has observed coexisting berylliosis and lung cancer in humans. Hueper, noting the established occupational as well as general environmental occurrence of human berylliosis, stated:

"If these manifestations should be followed by the development of cancers of the bones and lungs, the establishment of causal relations between a previous exposure to beryllium and the subsequently appearing cancerous reaction would appear to be rather easy."

V-B-6

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## 2. Organic Chemicals

### a. Combustion and Distillation Products of Coal

While coal (and perhaps graphite dust) is not considered as a respiratory carcinogen, the same cannot be claimed for the products of incomplete combustion, distillation and hydrogenation of coal. The carcinogenic action of these combustion and distillation products of coal on the skin of man and experimental animals has been established beyond doubt.

Hueper (970-B) has noted with respect to lung cancer, that:

"The human evidence relating exposure to coal tar and pitch, dust and fumes, with an increased liability to cancer of the lung is not extensive and is in part controversial."

With respect to lung cancer deaths among members of different occupational groups exposed to various types of coal tar, an above-average lung cancer frequency has been observed in England, Canada, and Japan (243, 987-A, 1759). Commenting on this evidence, Hueper (970-B) said:

"...it appears that the inhalation of tar fumes sustained by workers of certain operations seems to have an excessive liability to cancer of the respiratory tract."

(See also the section herein on Biological Studies.)

V-B-7

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b. Petroleum, Shale Oil and Natural Gas

The carcinogenicity of certain high boiling fractions of petroleum and oil shale, as well as of the combustion products of these petroleum derivatives, such as shale oil and natural gas, has definitely been demonstrated not only on experimental animals but also on workers developing skin cancers after prolonged contact with these agents.

In addition to skin contact with carcinogenic petroleum derivatives, many workers are also exposed for occupational reasons to an inhalation of oil mist or fumes. A few cases of lung cancer have been reported. Hence, the occupational evidence available (or published) on this aspect of lung cancer is rather scanty and in part controversial.

V-B-8

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### 3. Polymeric Material

#### a. Asbestos

Inhalation of long-fibered asbestos produces asbestosis. The co-existence of asbestosis and lung cancer was first reported in 1935 and since that time some 80 cases of asbestosis lung cancer have been recorded. Although some authorities have refuted the causal relation between asbestosis and lung cancer, the West German Government has recently made asbestosis lung cancer a compensable disease. The procedures employed to refute this relationship are, according to Hueper (970-B), bound to give misleading results.

The experimental approach to date has yielded equivocal results: positive results in mice by Nordmann and Sorge (1400); negative results in guinea pigs by Vorwald and Karr.

V-B-9

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b. "Isopropyl Oil"

"Isopropyl oil" is a polypropylene and is the residue obtained in the preparation of isopropyl alcohol. Weil et al. (462) reported seven respiratory tract cancers among 71 workers (nasal sinus, 4; larynx, 2; lung, 1) working 5 years or more in this industry. Since that time, 5 additional cases have been reported (larynx, 4; lung, 1).

Weil et al. (462) also demonstrated the carcinogenic activity of "isopropyl oil" in experimental animals both to mouse skin and to mouse lung.

V-B-10

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C. GEOGRAPHICAL FACTOR

The study of the geographical distribution of lung cancer can hardly be said to have shed much light on the etiology of the disease other than to give support to the belief that environment is a factor. Steiner (1980-A, 1980-B) says:

"A strong case can be made from the geography of lung cancer for an etiological importance of environmental carcinogens. This hypothesis appears to explain best the differences between cities or other regional units within countries. It is impossible, however, to exclude the possibility of other etiologic factors. The changes in frequency within members of a race when they change environment by migration indicates that exogenous factors exist. On the other hand, the possibility remains that differences exist in sensitivity of cells of different persons to neoplastic conversion, as exemplified by the lung cancers in infants. No single explanation adequately accounts for the origin of all lung cancers."

Steiner has shown that no major area of the world is free of lung cancer, and that within most countries even the smaller geographical units contain examples of it. The disease also is probably present in various animals in all parts of the world. He notes that when lung tumors in mice were first described at the turn of this century they were found almost simultaneously in the United States by Livengood in 1896, in France by Haaland in 1905, and elsewhere,

V-C-1

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indicating that whatever the etiological factor might be it had already been widely disseminated. The evidence is as yet inadequate in Steiner's opinion to determine whether incidence is greatest in those species sharing man's environment most intimately, such as dogs and cats. According to him, dogs and horses have the highest species total cancer incidence, but he cautions that the older biological age of these animals might be the explanation. He deduces from the omnipresence of lung cancer in man and probably also in animals that an etiological factor is everywhere present and that whether it be genetical, chemical, physical, viral or some other factor the cause is everywhere in threshold levels (cf. section on Epidemiological Studies).

Steiner points out that although many papers have been written purporting to show geographical differences in incidence of cancer few deal specifically with lung cancer. He writes that in 1940 the reported death rate from all cancers per 100,000 population varied greatly between countries, running from a high of 176.0 in Switzerland to a low of 11.3 in Ceylon, and hazards the opinion that such large differences do not in fact exist and that the explanation for them is more likely to occur in considerations

V-C-2

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apart from true cancer frequency, such as the age factor and differences in accuracy of diagnosis and reporting. He believes that such comments are as applicable to lung cancer as to all cancers.

Steiner has shown a high frequency of lung cancer in Mexican women dying in the Los Angeles area. In 35,293 necropsies performed at the Los Angeles County Hospital from 1918 to 1947 on members of several ethnic groups, of which the Caucasoid and Mexican were the two largest, Mexican men had only slightly more lung cancer than Caucasoid males, but Mexican females had two times more than Caucasoid females and nearly as much as Mexican males. No data are available from Mexico for comparison. Similarly, Steiner says that the Negro residing in the United States and in the Caribbean area appears to have a higher frequency of lung cancer in necropsies than does the African Negro. As Steiner points out, this finding raises the question whether the disease is being insufficiently diagnosed in Africa or whether there has been a real increase since migration to America. He suggests that such an apparent increase, together with a similar increase in gastric cancer combined with a decrease in liver cancer seem to indicate that these varieties of cancer are determined, "at least in part," by environmental factors.

V-C-3

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Eastcott (923) studied the lung cancer incidence in New Zealand of immigrants from the United Kingdom, comparing them with native born New Zealanders of the same stock, and found a higher incidence among the immigrants. The difference was greater for those aged 30 or more when they emigrated to New Zealand. It was the same for women as for men and was consistent at all ages over 35 and for all the principal parts of the country. Eastcott concluded that the observed increased incidence was unlikely to be an artifact, for it was not seen in any of the other principal sites for cancer, and was equally unlikely to be attributable to cigarette smoking in view of the evidence available on the consumption of tobacco in the two countries during the first half of this century.

V-C-4

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#### D. SOCIOECONOMIC FACTOR

Socioeconomic distributions of cancer of the lung have been described by Cohart (902-B), who found that the incidence of lung cancer was more than 40 percent greater among the poor than among the other socioeconomic classes in a population group studied in New Haven, Connecticut. The meaning of this finding depends of course upon the smoking habits of the various socioeconomic classes. That is to say, if the less well-to-do classes smoke an amount that is equivalent to or less than the amount smoked by their social and economic peers, Cohart's finding suggests the absence of an association between smoking and lung cancer; if they smoke more, his finding supports an association. Kotin (982) classified the study of Cohart (902-B) as "limited."

Clemmesen and Nielsen (1552) found a clear tendency toward a greater incidence of lung cancer among males in the poorer social classes in Copenhagen for the period 1943 to 1947.

With respect to socioeconomic studies, Cornfield, et al. (3409) stated:

"The existence of other important lung cancer effects associated with such characteristics as socioeconomic class cannot be questioned. Cohart (902-B) found that the lowest economic class had a 40 percent higher lung cancer incidence than the remaining population of New Haven, Connecticut. Similar results from

V-D-1

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the 10-city morbidity survey (3422) have also revealed a sharp gradient in lung cancer incidence, by income class, for white males, which is consistent with Cohart's findings (902-B). Since cigarette smoking is not inversely related to socioeconomic status, we can agree with Cohart (902-B) '\* \* \* that important environmental factors other than cigarette smoking exist that contribute to the causation of lung cancer.'"

Cornfield, et al. (3409), noted that these and other findings are convincing evidence for multiple causes of lung cancer. Cornfield et al. argue that the effects associated with socioeconomic class and related characteristics are smaller than those noted for smoking history, and the smoking-class differences cannot be accounted for in terms of these other effects.

In this connection, Cornfield et al. (3409) have apparently overlooked an interesting observation by Mills and Mills-Porter (288) in their study of tobacco habits in an American city. Those writers found that cigarette smoking in Columbus, Ohio was more common in poorer, dirty sections than in clear, suburban areas, and that the reverse was true in the case of cigar and pipe smoking.

Potter (334-A), however, noted that the incidence of cancer of the stomach in the continental United States had decreased during the period 1933-1944. Potter considered that the stomach might be the site that would

V-D-2

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best reflect any correlation between lower incidence and improved standards of living, especially in the lowest economic group where the greatest improvement in dietary habits had occurred. In this study the incidence of cancer of the stomach decreased while that of cancer of the lung increased!

Kennaway [BRIT. J. CANCER, 4, 158- 172 (1950)] in a review of the data relating to cancer of the General Registrar Office in the United Kingdom could not discern any influence of social class upon the liability to lung cancer.

V-D-3

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E. SUMMARY

Any effort to incriminate atmospheric pollution as being responsible for lung cancer must contemplate the possibility that the opposition will concede the guilt of polluted atmosphere but contend that smoking has a cocarcinogenic effect. There is some suspicion to support the claim that tobacco smoke may be a cocarcinogen. Thus smoking would be called upon to share responsibility for lung cancer even though not in itself carcinogenic. The possibility also exists that smoking will be charged with a cumulative role or with being privy to a synergistic effect, but of course these two alternatives presuppose tobacco smoke to be or to contain a carcinogen.

Unless proof can be obtained to establish that tobacco smoke is neither carcinogenic nor cocarcinogenic, the best use of the theory that atmospheric pollution is capable of accounting for the increase in lung cancer would appear to lie in the position that data of an inconclusive nature (i.e., statistical studies, equivocal animal experiments, etc.) point to both smoking and air pollution (as well as to socio-economic differences and to geographical factors) and hence smoking should not be singled out. An alternative possibility is suggested by the fact that laboratory experiments involving inhalation

V-E-1

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of polluted atmosphere by animals have produced lung tumors whereas inhalation of tobacco smoke has not unequivocally done so. Similarly, powerful carcinogens have been identified in the atmosphere created by industrialization that have not been found in tobacco smoke. An example of these is the oxygenated aliphatic hydrocarbons found by Kotin; there is no reason to believe, however, that these cannot be found in time in tobacco smoke.

V-E-2

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## VI. THE PATHOGENESIS OF CANCER

Pathology is the science treating of diseases and their nature and causes. Pathogenesis is the genesis of a pathological process or disease.

This section will be largely limited to a description of those cellular changes which have been observed in the tracheobronchial tree of man and animals which have been thought by some to be precancerous. Emphasis will be placed on studies which inquire as to the effect of cigarette smoke, other inhalants, and factors such as chronic respiratory disease on the cell structure of man's trachea and bronchi. We shall also touch upon some of the work done in experimental carcinogenesis, from the point of view of tumor pathogenesis, that is, the neoplastic response of tissue to carcinogenic action. We shall not attempt to treat tumor etiology, consisting of the study of the carcinogenic agents themselves, their chemical interrelationships and their physical and chemical properties. The experimental carcinogenesis work we shall discuss is that thought to contribute particularly to our knowledge of the pathogenesis of tumors of the human larynx and tracheobronchial tree.

VI-1

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According to Greene, and some others, all the available evidence suggests that metaplasia is due to chronic irritation. Much of what follows will be a discussion of observations of various forms of metaplasia and attempts to relate the cell changes observed to precancer and to smoking. Some of the work in this field, such as that of Auerbach et al. (870, 870-A, 1204-A, 2111) and Szolomajer (3809), has been instituted on the assumption that there may be a parallel between metaplasia and lung cancer. Such an association has been postulated on the basis of the claim that metaplasia is the forerunner of squamous (having the appearance of fish-like scales or plates) cell carcinoma in the uterine cervix (cf. 3809). But Greene (1664) has spoken a word of caution in interpreting experiments relating metaplasia and lung cancer in excessive smokers. He makes the following points:

- (1) Winternitz of Yale observed an extreme degree of metaplasia in the lungs of people who died in the great influenza epidemic of 1917. Winternitz said at that time that if this was a precancerous lesion, then all individuals who recovered from influenza would subsequently die of lung cancer.

Obviously, as Greene observes, that has not occurred.

(2) The diagnosis of a lesion as precancerous is based purely on assumption and not on observation. The assumption is that the lesion would become cancerous if allowed to develop, but this is not possible because the tissue has been killed and stained in order to be seen by the pathologist and hence has no opportunity to develop.

(3) The term carcinoma-in-situ, or a noninvasive carcinoma, has come into frequent use. The term in Greene's estimation is "a complete absurdity". Since carcinoma is by definition an invasive lesion, a non-invasive carcinoma is meaningless. Although some believe that the cell appearance characterized as noninvasive carcinoma is precancerous, Greene adverts to the experience of a number of women subjected to cervical biopsies six or seven years ago, who refused surgical removal. He said that in the majority of those cases the same so-called precancerous lesion is present or has completely disappeared,



but that in only a very few instances has a cancer appeared.

(4) Not all chronic irritations will produce metaplasia. The nature of the irritant is of importance, as is the constitutional make-up of the individual. Moreover, not all areas of metaplasia resulting from chronic irritation are precancerous. Almost any adult in a post-mortem examination would show areas of metaplasia or areas that could be interpreted as precancerous, yet it is obvious that all will not die of cancer (cf. Weller, infra). Consequently, according to Dr. Greene, not all metaplasia can be considered precancerous.

A. Observations of Changes in Cell Structure and Interpretations of the Meaning Thereof

The investigations revealing changes in the cell structure of the human respiratory system presumably produced by various insults have all been reported during the past decade. Since the reports of these data tend to overlap chronologically, we have presented them alphabetically by author, as follows:

1. Auerbach et al. (U. S. A.)
2. Black and Ackerman (U. S. A.)
3. Chang (U. S. A.)
4. Chayen et al. (England)
5. Hamilton et al. (Canada)
6. Hilding (U. S. A.)
7. Kotin et al. (U. S. A.)
8. Sanderud (Norway)
9. Szolomajer (U. S. A.)
10. Weller (U. S. A.)
11. Wittekind and Struder (Germany)

1. Auerbach et al.

Auerbach et al. observed changes in the bronchial epithelium (the lining of the bronchial tree) in a man with bronchogenic carcinoma who had been exposed to chrome (an established carcinogen)

for many years prior to his death, which prompted them to postulate that if smoking is a factor in human lung cancer then there should be changes in the bronchial epithelium in cases of bronchogenic cancers and in moderate as well as heavy smokers that are different from those of non-smokers. They anticipated that inquiry would disclose a greater incidence of squamous metaplasia in moderate and heavy smokers than in non-smokers since squamous cell carcinoma is the most frequent type of human lung cancer observed.

In a preliminary paper published in 1956 Auerbach and associates (870-A) reported the results of their statistical study of the tracheobronchial tree in 41 cases, of which 8 were non-smokers, 14 light to moderate smokers, 5 heavy smokers. Of the 41 cases studied, 14 had lung cancer; all of these had been moderate to heavy smokers. Three types of epithelial changes were evaluated: basal-cell hyperplasia, stratification, and squamous metaplasia. Basal cell hyperplasia was present to a greater degree in smokers than in non-smokers. Stratification and squamous metaplasia were present to a slightly greater degree in smokers than in non-smokers. The authors recognized the necessity for more extensive

VI-A-2

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study using more cases. Parenthetically, they acknowledged that the only report in the literature in which an attempt had been made to determine whether smoking produces definite epithelial changes (Wittekind and Struder - see, infra) concluded that there was no relationship between tobacco smoking and metaplasia but that metaplasia was related to chronic bronchitis.

The tracheobronchial tree is composed of three types of cells--the ciliated columnar cell (the cells containing the minute hair-like processes known as cilia), the goblet cell (the cells near the surface which generate mucus), and the basal cell (the cells immediately below the columnar and goblet cells). The latter lie along the tunica propria (an enveloping membrane or layer of tissue), usually as a single layer; they have a scanty cytoplasm and oval or round nuclei. Auerbach and his colleagues judged the extent of basal cell hyperplasia by the number of layers of such cells (hyperplasia being generally defined as an abnormal increase of the cells).

It is interesting to note that the data in the paper just described were originally presented by Auerbach before the American College of Chest

VI-A-3

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Physicians in June, 1955. At that time, the paper had one interesting sentence - which later was deleted from the published article:

"We began this study with the preconceived notion that, since squamous cell carcinoma is the most frequent type observed, we should see a greater incidence of squamous metaplasia in moderate and heavy smokers than in non-smokers."

Some of the deficiencies of this study either noted by us or admitted by Auerbach himself are as follows: (1) only smoking habits were considered; (2) the observations of the slides were, of necessity, two dimensional; (3) the smoking histories accepted were those reported by the deceased's relatives rather than those appearing on the deceased's hospital chart; and (4) age and sex were not considered as factors. It is also worth noting that the paper does not describe the procedure employed in the selection of the sections, i.e., whether the sections taken were randomly distributed throughout the sample or whether they were adjacent samples from the same block of epithelium.

In a subsequent paper, presented before the Third National Cancer Conference in 1956 (870) and published in 1957 (1204-A), called a progress report on their study of changes in the bronchial epithelium in relation to smoking and lung cancer,

Auerbach et al. reported the results of histopathologic observations of the tracheobronchial tree in 117 cases. This study was undertaken to test two hypotheses postulated by Auerbach and his associates:

(1) If inhalants are a major factor in lung cancer one might expect to find hyperplasia, metaplasia and early neoplastic (pertaining to malignancy) changes in the remaining bronchial epithelium of people who had died with bronchogenic carcinoma.

(2) One would also expect to find similar changes, but to a less marked degree, in the bronchial epithelium of persons who had died of some other cause, but who had been heavily exposed to potential carcinogenic inhalants.

Since the study was not completed, Auerbach et al. set forth their findings and conclusions subject to modification.

The cases studied were divided into two categories: those who died of bronchogenic carcinoma (34 cases), all of whom were smokers, and those who died of other causes. The latter were graded according to smoking histories into three groups, namely, those who never smoked regularly or at all (16 cases), those who smoked over a pack a day

(20 cases), and those who smoked more than a pack a day (47 cases). The following four changes in the epithelium were evaluated: basal cell hyperplasia; stratification; squamous metaplasia; and carcinoma-in-situ. These changes were observed in all groups, both smokers and non-smokers, but were least intensive in the group that never smoked regularly, with a progressive increase in findings in the moderate and heavy smokers. The same, but more extensive, changes were observed in those who died of carcinoma of the lung. Auerbach et al. also found an almost similar distribution of carcinoma-in-situ in those who smoked more than one pack a day (6.0%) as in the case of bronchogenic carcinoma (6.3%). They concluded that their findings were fully consistent with the hypothesis that inhalants of some sort are important in the causation of bronchogenic carcinoma as well as being consistent with the theory that cigarette smoking is important.

The following terms and definitions thereof were applied by Auerbach et al. to the changes observed in the tracheobronchial epithelium:

"(1) Basal Cell Hyperplasia: The basal cells lie along the tunica propria. They have scanty cytoplasm and small dark oval

VI-A-6

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or round nuclei. Since there has been some disagreement among histologists as to what constitutes the normal number of basal cells, only three or more rows of typical basal cells have been classified as basal cell hyperplasia.

(2) Stratification: The bronchial surface mucosa in cases of stratification showed an absence of the ciliated cells and some flattening of the epithelial cells toward the lumen. The process never involves all of the deeper layers.

(3) Squamous Metaplasia: In this group the epithelial lining is generally thicker and is made up of larger cells. It resembles squamous epithelium seen elsewhere in the body and involves the full thickness of the surface mucosa.

(4) Carcinoma-in-Situ: We have applied the same criteria here as are accepted for intraepithelial carcinoma in other sites in the body and as those applied by Black and Ackerman in their study of bronchogenic carcinoma, namely (a) The basement membrane is intact, (b) There is cellular disorganization with loss of the usual layering, (c) The nuclei show a great variation in size, shape and chromatin content. Nuclear hyperchromatism is frequent, (d) There is an increased number of mitoses and they are often atypical, (e) The nuclear-cytoplasmic ratio is increased, and (f) the epithelium is often, but not always thickened, a finding similar to that observed in the larynx by Stout; Altmann, Ginsberg and Stout."

Basal cell hyperplasia, stratification, squamous metaplasia and carcinoma-in-situ were diffusely distributed throughout the epithelium of the bronchial tree in both lungs as well as the trachea in those cases which succumbed to bronchogenic carcinoma. This, say the authors, is exactly



what one might expect to find if the fatal cancer were caused by some carcinogenic agent applied to the epithelium of the entire tracheo-bronchial tree. It is consistent, according to them, with the theory that the inhalation of carcinogenic substances in dust, vapor or smoke is a major factor in lung cancer etiology.

The four changes described were found to be, in the case of subjects who died of causes other than lung cancer, almost as common in the one pack or more a day cigarette smokers as in the case of those who died with lung cancer. These changes were less frequent in moderate cigarette smokers and still less frequent in men who had never smoked regularly. Auerbach et al. say that "the few changes noted in the lungs of some of the non-smokers as well as some of the changes present in the lungs of smokers were due in part at least to inhalents [sic] other than tobacco smoke". They reason that probably all of the men studied had been exposed in some degree to air pollution associated with urbanization, and express the hope that they will be able to find a series of subjects who never smoked and were never exposed to such air pollution.

VI-A-8

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Again, it may be noted that Auerbach et al. (870, 1204-A) considered smoking habits alone as a factor. Moreover, they say that the material was studied after the smoking histories had been obtained. They admit that all cases of deaths from lung cancer were included, whereas cases dying of other causes were included "only if an adequate smoking history could be obtained".

On the other hand they have met one of our objections to the earlier study in that they have in this experiment followed a systematic procedure in the selection of slides.

A third report from Auerbach et al. (2111) sought the answers to the following questions which arose in their previous study:

"(1) What is the incidence of carcinoma-in-situ in people with carcinoma of the lung? (2) What is the distribution of carcinoma-in-situ in the anatomic divisions of the tracheobronchial tree? (3) Does early invasive carcinoma occur in the remaining portions of the tracheobronchial tree? (4) Of what clinical value are these findings?"

An examination was made of the tracheobronchial trees of 54 white men who died with lung cancer, of whom 39 (72%) were in the age group 50 to 69 years at death. Carcinoma-in-situ occurred in 48 of the 54 cases (89%), the in-situ changes being

widely but somewhat irregularly present throughout all segments of the tracheobronchial tree. There was a comparable incidence of these lesions in the opposite lung as in the lung involved by bronchial carcinoma. Early invasive carcinoma was observed in 5 of the 54 cases. Notwithstanding the small number of cases in which early invasive carcinoma was seen, Auerbach et al. conclude that the presence of early invasive carcinoma in the region of carcinoma-in-situ suggests that the latter is a stage prior to invasion. Carcinoma-in-situ was defined in essentially the same fashion as in previous papers. Early invasive carcinoma was defined as extension of the changes seen in carcinoma-in-situ beyond the confines of the basement membrane. One is reminded of the warnings of Greene (see, supra) concerning the speculative nature of such diagnoses.

As to the clinical significance of carcinoma-in-situ the authors write:

"The question arises as to the clinical significance of carcinoma-in-situ. We concur with the statement of Black and Ackerman \* \* \* that carcinoma-in-situ of the uterine cervix has been linked with invasive carcinoma. Other investigators have followed the development of epidermoid carcinoma of the cervix from a study of serial biopsies over a period of several years \* \* \* They found hyperactivity of

VI-A-10

2025018494

the basal cells, followed by carcinoma-in-situ, and finally invasive carcinoma. Comparable changes in the larynx have been described by Altman, Ginsberg, and Stout, \* \* \* Miller and Fisher, \* \* \* and by Stout \* \* \*. It is our opinion that the same events take place in the bronchus and that carcinoma-in-situ is the pre-invasive stage of carcinoma of the bronchus. We feel that it occurs in multiple sites, and that the ultimate fate of all of these foci is a question which will require much study. However, there is evidence from this [sic] data that some of them continue on to frank invasive carcinoma."

See discussion of Black and Ackerman, infra.

They also observe that the low cure rate after pulmonary resection for bronchial carcinoma may be due to foci of carcinoma-in-situ developing in other areas which have progressed to the stage of carcinoma. They have no answer for the significant fact that although primary tracheal carcinoma is relatively infrequent they observed carcinoma-in-situ with equal frequency in the trachea as in the left main bronchus.

2. Black and Ackerman

Black and Ackerman (1502) have summarized some of the papers cited by Auerbach et al. (2111) as follows:

"Several investigators, working independently, have enumerated the following stages of development of epidermoid carcinoma of the cervix from a study of serial biopsies over a period of several years: (1) normal squamous epithelium, (2) hyperactivity of the basal cell layer, (3) epidermoid carcinoma in situ, and (4) invasive epidermoid carcinoma.

The evidence on which this synthesis is based is contained in the following observations: Younge \* \* \* reported 15 cases in which intra-epithelial 'anaplasia' (equivalent to advanced basal cell hyperactivity in our terminology) has been followed by epidermoid carcinoma in situ; in situ carcinoma is commonly found at the periphery of invasive carcinoma of the cervix; the site of predilection for both is the same (junction of the columnar with the squamous epithelium in the cervical canal); and a total of about 30 cases have been described \* \* \* in which carcinoma in situ of the cervix has been followed by invasive carcinoma. These observations are well documented and reported independently by qualified investigators, so that there can be little doubt that in the cervix, at least, this progression from basal cell hyperactivity to carcinoma in situ to invasive cancer exists.

Although others \* \* \* have previously described epidermoid carcinoma in situ in the bronchial epithelium in isolated cases, the relatively frequent occurrence of this finding in association with frankly invasive carcinoma has not been stressed \* \* \*"

In an original investigation, Black et al. examined microscopic sections from the lungs of 60 cases of epidermoid and undifferentiated carcinoma of the lung. The definition of carcinoma-in-situ employed by Black and Ackerman is that used by Auerbach et al. (see, supra for definition). They summarized and commented on their findings as follows:

"[We] have found unquestionable carcinoma in situ in 13 (22 per cent) and anaplastic hyperactivity of the intact bronchial epithelium in eight additional cases, or 13 per cent. Thus, in 35 per cent of the cases reviewed, either marked anaplasia of the intact epithelium or frank carcinoma in situ was found adjacent to invasive carcinoma of the lung. In all of these the tumor was central in origin, arising

VI-A-12

2025018496

in lobar bronchi or in one of their major segmental divisions. In addition, in all but seven (11.7 per cent) of the 60 cases, advanced squamous metaplasia of the bronchial epithelium was found. It should be emphasized that the microscopic sections reviewed were for the most part random ones and no consistent attempt had been made to demonstrate the epithelial changes at the periphery of the tumors. We therefore believe that a more intensive search might well reveal an even higher incidence of intra-epithelial cancer.

The association of marked squamous metaplasia of the bronchial epithelium and ducts of the mucous glands with carcinoma of the lung has previously been noted \* \* \* The mere occurrence of squamous metaplasia in association with carcinoma of the lung, however, cannot be regarded as anything more than an interesting coincidence, since a similar transformation from the tall, single-layered, columnar bronchial epithelium to stratified squamous epithelium has been observed repeatedly in a large variety of chronic pathologic processes in the lung. Prominent among these are severe bronchiectasis \* \* \*, lipoid pneumonia, tuberculosis, and chronic lung abscess. It is common knowledge that these lesions are only rarely precursors of carcinoma of the lung. \* \* \*

Although squamous metaplasia alone probably does not give rise shui [sic] generis to frank bronchogenic carcinoma, we have learned to associate increased activity of the basal [sic] cell layer with frank invasive carcinoma at some nearby site in a significantly large number of cases \* \* \*."

The authors considered their findings in the lung to be somewhat different from those observed in the cervix:

"The presence of malignant transformation of the glandular epithelium does not represent true invasive carcinoma (as argued by TeLinde in the case of carcinoma of the cervix) for the basement membrane is still intact, \* \* \*."

In their study Black and Ackerman noted, in addition to intraepithelial carcinoma of the bronchus at the

VI-A-13

2025018497

periphery of the clinically obvious lung carcinoma, multiple areas of "preinvasive malignant change at some distance from the tumor" which they termed "a particularly disturbing feature" of the process.

They concluded on the basis of their study:

"\* \* \* evidence has accumulated that epidermoid and undifferentiated tumors of the major bronchi may arise first as islands of carcinoma in situ. The initial stage in this process is a progressive metaplasia of the surface epithelium with cellular hyperactivity in the basal layer. Statistically speaking, this process appears to be an important one, since examples of it were found in 35 per cent of 60 unselected epidermoid carcinomas of the lung. Epidermoid carcinoma in situ may be present at the periphery of an invasive tumor or appear at multiple sites either in the same lung or in other portions of the tracheo-bronchial tree. The discovery of such a process almost invariably indicates an invasive tumor nearby \* \* \*"

### 3. Chang

Chang (565, 900, 2068, 2158, 2486) (dated 1956 to 1958) conducted a study of whole mounts, as well as sections, of the human bronchial epithelium in an effort to shed light on the question whether "excessive" cigarette smoking over long periods of time "promotes" the development of bronchogenic carcinoma. In the introduction to his paper he accepts two propositions, viz.: that lung cancer is more frequent in heavy cigarette smokers, and that "burned cigarettes" contain materials which are carcinogenic when concentrated and applied to the skins of mice. He apparently assumes that

VI-A-14

2025018498

these two propositions establish smoking as a cause of lung cancer, for he moves immediately to the question whether smoking is the only cause: "But it does not follow that heavy cigarette smoking is the only cause of bronchogenic carcinoma."

Chang's technique is to study the frequency of epithelial lesions that might be precancerous in males and females, smokers and non-smokers, in the ages of incidence of bronchogenic carcinoma. He says this is important because "it is possible that products of burning cigarettes serve as promoters of carcinogenic action perhaps as well as true carcinogens" (cf. Gellhorn (2780)).

The advantage of the use of whole mounts is in the opportunity it offers to study sets of bronchial epithelium several layers thick, whereas only the surface view can be seen in vertical sections. Chang points out that one can scan fairly large areas of epithelium for local areas of hyperplasia and hypoplasia (arrested development of the tissue), for alterations in the relative numbers of goblet, ciliated cells, and invading leucocytes (white corpuscles). On the other hand, he concedes more cellular details are visible in sections.

Chang summarized his findings with respect to the 105 autopsy cases, both male and female (consisting of 34 non-smokers and 71 smokers, all over 40 years old),

VI-A-15

2025018499



substantially as follows:

Epithelial whole mounts of non-smokers generally showed fewer distended goblet cells than those of smokers. In the latter, numerous distinct goblet cells were present, fairly well distributed over the entire surface. The same classification of individuals as to smoking habits was adopted as that used by Watson and Conte (460, 719-A). In some chronic heavy smokers who had smoked more than 30 years he found distinctive cellular irregularities, inter-cellular spaces, hyperchromatism (excessive pigmentation), variable mitotic (pertaining to indirect cell division in which complex nuclear processes precede the dividing of the cytoplasm) figures with atypical nuclei, which Chang considers to be either early stages of metaplasia or pre-cancerous lesions since their occurrence is similar to those of true carcinoma. In cases of bronchogenic carcinoma where there was a history of long smoking, the appearance of whole mounts was "peculiar". The surface of the epithelium was uneven and coarse furrows were observed; the nuclei were enlarged and no goblet cells were seen.

The average length of cilia in non-smokers was longer than in smokers, and the average thickness of the epithelium in non-smokers was less than that in smokers. But there were exceptions in which some smokers' ciliated epithelium looked much like that of non-smokers'.

VI-A-16

2025018500

Basal cell activity, epithelial indentation and intraepithelial inflammatory cell infiltration were more conspicuous in smokers than in non-smokers. The occurrence of atypical cells with giant, bilobed, binucleated or multinucleated, large nucleoli and binucleoli or multinucleoli was more frequent in smokers than in non-smokers. Most of these atypical cells may never become malignant, says Chang, but some of them seem to him "to be the course of carcinoma in situ or of invasive carcinoma."

The incidence of bronchial metaplasia was 37.1%. Chang says, however, that it is likely that the actual incidence having in mind the whole bronchial tree is much greater, since only a relatively small area of bronchial epithelium was examined. The metaplasia observed was more frequent in smokers than in non-smokers and in males than in females. The age of maximum frequency was 50 to 69 years.

Lesions of the respiratory system (pathological controls) were more frequent in smokers than in non-smokers, but most of these lesions were not accompanied by bronchial metaplasia except bronchogenic carcinomas.

#### 4. Chayen et al.

Auerbach's work in part prompted some English pathologists to conduct a histochemical investigation to determine whether the proliferation that may occur in the

VI-A-17

2025018501

cells of the basal layer without other histological abnormality might be related to the development of bronchial cancer. Experiments by Chayen et al. (3571), the report of which was published in 1959, have shown a very marked increase in the content or availability of lipid (which is defined as any of a group of substances comprising the fats and other esters that possess analogous properties, being characterized by solubility in fat solvents, by insolubility in water, and by their greasy feel), said by Chayen et al. to be probably bound phospholipid, as shown by coloring with Sudan Black and staining by the acid haematein method (a standard tissue dyeing method). This effect was strongest in the nuclei of the basal cells and was particularly well seen in the condition known as basal cell hyperplasia. In contrast, scarcely any lipid could be demonstrated in the cells of foci of established squamous metaplasia.

Since basal cell hyperplasia and other proliferative changes are common in smokers who exceed 40 cigarettes a day, Chayen and associates write, it seemed worthwhile to them to see if similar histochemical disorders occurred in histologically normal areas of bronchial epithelium in such persons. They demonstrated an increased lipid content in the basal cells, particularly in the nuclei, of otherwise normal bronchial epithelium from such smokers, in chemically normal epithelium from non-smokers only the nucleoli in the

VI-A-18

2025018502

basal cells are stained.

Chayen et al. also treated sections with an aqueous solution of 3,4-benzpyrene, and the distribution of this fluorescent carcinogen was followed by fluorescence microscopy. Those cells which gave a positive reaction with the acid haematein method also showed selective absorption and concentration of 3,4-benzpyrene, especially into the nuclei.

They expressed the opinion that, if their observations on fixed cells can be extrapolated to the living epithelium, it would appear that bronchial cancer is produced in two main stages: damage to areas of epithelium, possibly by cigarette smoking, altering them so as to increase their affinity for lipid-soluble substances, followed by preferential absorption of carcinogenic hydrocarbons. Finally, they observed that these events need not necessarily occur in every focus of proliferation, and that the development of bronchial cancer might also be affected by local differences in the concentration of carcinogens accumulating in the vicinity of the foci. The circumstances influencing the local concentrations are probably complex and include, in the opinion of Chayen et al., such factors as stagnation of mucus and loss of cilia.

VI-A-19

2025018503

5. Hamilton et al.

Hamilton et al. (2242) in a paper published in 1957 reported the results of observation of one lung in 65 subjects. The right lung was arbitrarily chosen except in cases of carcinoma of the lung in which event the opposite lung was used. The cases were divided into three groups, namely, 30 of lung cancer, 15 of smokers who did not develop cancer, and 20 of non-smokers. Five types of epithelial change were observed: basal cell hyperplasia, stratification, squamous metaplasia, transitional metaplasia, and intermediate change. The first of these was the most common finding, and was more extensive and encountered in a significantly higher percentage of smokers' lungs, including those with cancer. The other changes showed only a slightly higher incidence. Hamilton et al. write that with the exception of basal cell hyperplasia, the changes described in bronchial epithelium have been observed in association with chronic inflammatory changes in the bronchial wall (cf. Weller and Wittekind et al.). However, they say, the significant difference in incidence and extent of basal cell hyperplasia in cases of lung cancer and in smokers cannot be explained on the basis of inflammation.

With respect to their findings, the authors wrote:

"Our data do not lend themselves to any further analysis of etiological factors which may have induced the morphological alterations, and the only fact which has emerged is that basal cell hyperplasia of bronchial epithelium is more common in smokers,

VI-A-20

2025018504

but we cannot ascribe this change to smoking alone, nor can we suggest that it has any relationship to cancer."

6. Hilding

Hilding (1359-A, published in 1957) has studied the ciliary mechanism in an effort to determine how it normally removes foreign substances and to see how inhaled carcinogenic substances might accumulate and pause at certain spots for a time sufficient to supply the chronic irritation frequently cited as necessary in the development of cancer.

The material with which Hilding worked was the respiratory tracts of humans, cows and calves removed at autopsy and examined as soon after death as practicable. As described by Hilding, a thin film of rather viscid mucus overlies the ciliated respiratory epithelium; this blanket, moving continuously upward toward the larynx, motivated by ciliary action, constitutes the ciliary stream. The cilia (the minute hair-like processes) are capable of a vibratory or lashing movement and extend down as far as the bronchioles, where the ciliary stream presumably begins. Since the cilia continue their activity for many hours after death, Hilding was able to observe ciliary streaming, the flow being made visible by applications of droplets of India ink to the surface of the mucous blanket.

Hilding claims it as a fact that a substantial part

VI-A-21

2025018505

of the visible smoke from cigarette smoking is deposited in the lower respiratory tract upon and in the mucous blanket, wherever the inspired air flows. Part is dissolved and absorbed and the rest is carried away with the mucous blanket in the ciliary stream to the esophagus. According to Hilding, the ciliary stream begins in the respiratory bronchioles in a stream bed that is, in the aggregate, meters in extent taking into account the relatively large number of bronchioles. In the short distance from the bronchioles to the coryna (the junction of the bronchi to form the trachea), the stream narrows to about 2 in., which is the circumference of the trachea. Hilding further observes that the volume of mucus flowing over a unit area increases as the stream bed narrows, and that this increase is further enhanced by any additional mucus secreted by the glands en route. It is probable, he says, that the velocity of flow also increases as the stream bed narrows.

Hilding claims it is certain that the ciliary stream encounters a number of obstructions over which, or past which, it must flow in its course from the bronchioles to the esophagus. Among these he numbers the openings of the tributary bronchi (which also narrow the stream bed at the point where they join the bronchi), the squamous epithelium of the vocal cords, normally occurring squamous islands or areas of metaplasia, and any other normal or abnormal areas that are devo-

VI-A-22

2025018506

of cilia. Hilding observed that at the vocal cords and at each bronchial opening the axial progress of flow in his specimens ceased, and the mucous blanket was split in two parts to flow in opposite directions at approximately right angles to the previous directions of flow. In the human he claims it would be certain that the same phenomenon occurs at the bronchial openings and that it is a reasonable assumption that it occurs at the vocal cords. This altered direction of ciliary streaming depends in his opinion upon a change in the direction of ciliary beat and upon traction on the mucous blanket, which in turn depends upon viscosity of the blanket and relative activity of cilia in the area.

On the basis of his findings Hilding suggests there are the following possibilities for comparative stasis and prolonged action of carcinogenic substances deposited in the ciliary stream, in keeping with the chronic irritation theory:

"Where the mucous blanket divides in the middle of the bronchial lip (septums).

In whirlpools that may occur just where the four-way split of the two mucous blankets of joining bronchi occurs -- here the chemical action would be favored by stirring.

Upon the squamous islands or areas of metaplasia that are known to occur in many persons.

Upon the vocal cords where squamous epithelium is encountered -- especially anteriorly, where the mucous blanket must split."

He reasons that if the slowing or comparative statis

VI-A-23

2025018507



described above occurred habitually in a smoker, at any one of the points mentioned, the conditions of the skin experiments, in which carcinoma is produced by coal and tobacco tar painted on the skins of laboratory animals for a third to a half of their life span, might be closely simulated in the human smoker. Moreover, Hilding believes that the distribution of squamous cell carcinoma in the respiratory tract suggests a relation to the ciliary stream. Such cancers, he points out, are apt to occur among the larger bronchi, which is where the ciliary stream has been gathered from a wide stream bed to a narrow one and where obstructions in the form of bronchial openings and squamous islands occur. On the other hand, they do not commonly appear in the trachea, where the flow is more uninterrupted, but do occur again upon the vocal cords where the squamous epithelium obstructs the flow. Hilding adds that the possibilities suggested by his experiments apply to any inhaled, slowly acting carcinogenic substance and are by no means limited to cigarette tar.

In a paper published in 1956 Hilding (965-A) reported the results of experiments conducted with the lungs of freshly killed cows in an effort to determine how much of the cigarette smoke deposits in the tracheobronchial tree, how much returns with expiration, where it might deposit, and how rapidly it deposits, if deposition occurs. A smoking apparatus was devised to simulate the pressures and puffs used by cigarette smokers, which delivered smoke into the

VI-A-24

2025018508

bovine lungs under conditions thought by Hilding to be comparable to human smoking habits. He did note, however, that the smoking apparatus delivered more smoke than smokers return with expiration. Presumably he means by this that his experiments should be more accurate than similar experiments which have been conducted by means of collecting the cigarette smoke in the mouth or respiratory tract of humans and then blowing it into the experimental animal or autopsy portions of animals.

Hilding noticed that when the smoke delivered into the tracheal end of the respiratory tract of the cows emerged from the larger bronchi at the cut surface of the lung (the bottom half of which had been cut off by Hilding) it was much less dense and more blue than when passed into the trachea. He claims to have noticed that a large proportion of it was deposited on the walls of the air passages in the form of a thin, brownish-yellow film, the greater deposit being at the proximal end of the trachea, diminishing progressively toward the coryna. He could not detect this film in the bronchi, because, in his opinion, most of the tar had been deposited before the bronchi were reached and also because the tar deposit is spread more thinly as the deeper parts of the respiratory tract are reached as a result of the increasing area of the mucous membrane.

When Hilding clamped the larger bronchi, thus

VI-A-25

2025018509

forcing the smoke and air to pass through smaller bronchioles, the smoke was filtered out so completely that it was not visible. From this he concluded that if these observations are comparable to man, the smoke reaching the tiny air passages of the lung is largely deposited and what returns with expiration is mainly the amount that lies in the larger air passages. Perhaps, says Hilding, little or no smoke actually reaches the alveoli.

He concludes, on the basis of his experiments, that it is only a matter of seconds for the tar to deposit, and that there is no reason to believe tar is not deposited equally quickly in a smoker's lungs. Hilding believes that a portion of the deposit on the mucous blanket dissolves quickly and enters the ciliated cells. If sufficiently concentrated this toxic material destroys ciliary action. Nicotine, alone or in combination with other unnamed toxic materials, is possibly responsible for this action according to him. If, on the other hand, ciliary action is not destroyed then he believes that the tar is carried along with normal ciliary streaming and eventually delivered into the laryngeal pharynx from which it proceeds into the stomach. Hilding refutes the idea that the dissolved toxic materials which he believes to be present in cigarette tar could be sufficient to stop ciliary action altogether because cessation of ciliary activity is not compatible with survival.

VI-A-26

2025018510

Another paper published in 1956 records Hilding's findings with respect to the accumulation of cigarette tar upon artificially produced deciliated islands in the respiratory epithelium (965-B). Again he worked with the trachea, bronchial tree and lungs of freshly killed cows, this time in an effort to relate ciliary action to bronchogenic carcinoma. More precisely, he started out to see if the deposit of tar from cigarette smoke is analogous to the skin painting experiments applying tar to mice. In view of his previous experiments he says that if the tar is deposited in a thin film on the bronchial tree of a smoker (as in the case of experiments with cows) the film must either be absorbed or moved with the mucous blanket. He says it does not seem likely that all or even most of the smoke deposit is absorbed. Consequently, he believes it likely that the tar is removed with the mucous blanket through ciliary action.

Hilding says that in general those areas in the nose which are exposed to impact from inspired air will, by direct flow or by means of eddies, tend to become nonciliated, and the epithelium is found to be squamous or transitional type rather than columnar. He refers to studies in which air flow through the nose was altered by closing one nostril in experimental animals; these indicated that the distribution of such squamous-like epithelium can be altered or extended by changing its exposure to inspired air. He says, however,

VI-A-27

2025018511

that there are no large nonciliated areas below the vocal cords comparable to those found in the upper respiratory tract, but that there are islands of squamous epithelium or metaplasia devoid of cilia. According to one study, Hilding says, they have been found in as many as 32% of adults, and may possibly be present in everyone; whether present at birth or developed in post-natal life from impact of inspired air or other causes is not known. By artificial means (physical), deciliated islands were created from which the surface ciliated cells were removed or destroyed and only the deeper replacement cells remained. In separate experiments (using separate specimens) the ciliary streaming with relation to these islands was observed using India ink and cigarette tar. In the experiments with the former substance the ink collected upon all but 4 of between 30 and 35 artificially deciliated islands, stopping at and accumulating across the deciliated island in the form of a black crescent and remaining there for the duration of the experiment. On the other hand, much of the ink flowed around the islands and proceeded to the upper end of the trachea. Since the artificially deciliated islands were not comparable to natural islands of metaplasia (in that the latter are presumably covered with the mucous blanket), the artificial islands in some specimens were again covered with mucus by dropping an accumulation of it (collected near the larynx)

VI-A-28

2025018512

on the mucous surface upstream from the island. Eventually it moved across the island, leaving the island covered with mucus. The experiments repeated with ink gave essentially the same results as before except that the ink crescent did not seem to be quite so large or dense and was more readily dragged away by adjacent ciliary action.

The experiments with cigarette tar were conducted with the tracheobronchial trees and lungs from calves rather than cows. After removal of the lower third of each lung the trachea was attached to the smoking apparatus and smoke delivered. Immediately after the smoke had been passed small spots of mucosa were deciliated as in the first experiment, this time through openings in the trachea. A total of 39 deciliated islands was prepared in the 6 specimens used. Five of these islands were observed to be marked by small masses of tar-containing mucus. Two were in the trachea and both in the same specimen. The other three were in the main bronchi, two of them in one specimen. In two others there were small masses of mucus which may have collected because of the deciliated islands, but Hilding was not sure. The two accumulations in the one trachea were especially remarked upon by Hilding because he said they resembled the ink crescents closely.

Hilding acknowledges that India ink is not cigarette tar and that a deciliated island is not the same as a

VI-A-29

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squamous island.

Yet with only the rather scanty evidence provided by the cigarette tar experiments, Hilding reasons as follows: Ciliary streaming in both sets of experiments was slowed down at the deciliated spots so that it took hours instead of minutes to clean them. The smoke is deposited in a thin, rather even film upon all exposed mucous surfaces (not so according to his earlier experiments (965-A)). Those compounds which are readily soluble are quickly dissolved in the mucous blanket and may quickly act upon the local cells or be absorbed (there is no evidence of this in his experiments). Such action would be widespread and the concentration of the chemical compounds probably would be much the same everywhere (this does not explain the infrequency of cancer of the trachea).

With relatively insoluble or slowly soluble compounds, he says the story would be quite different. They might be removed from the tract entirely by ciliary action before dissolution and before having an effect on the cells, unless the blanket should stop at some point, such as the deciliated islands, where accumulation could occur. In this event the action of slowly soluble chemical compounds upon the cells in the islands would obviously be greatly increased. Under such circumstances Hilding believes that the conditions of the production of experimental cancer on the skin of

VI-A-30

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animals by tar would be closely duplicated. He now rejects his former thesis that tar might be deposited in quantities sufficient for carcinogenesis at points of impact by inflowing air during inspiration, as being much less likely in the light of these experiments. Finally, he acknowledges that the piling up of noxious material on nonciliated islands could be the key to carcinogenesis from any inhaled carcinogenic substance of whatever nature.

7. Kotin et al.

In a paper published in 1959, designed as the first of a series of three on the role and action of environmental agents in the pathogenesis of lung cancer, Kotin and Falk (3474) reported the results of atmospheric-type irritant substances (ozone, gasoline, aldehydes, organic acids, etc.) on the normal functions of the tracheobronchial tree. The subsequent papers in this series have not appeared to date.

Two types of studies were undertaken. First, animals in inhalation chambers were exposed to control test environments for varying periods. After the animals were removed, the tracheobronchial trees were exteriorized and opened so that ciliary activity and mucous secretion could be observed in the living animal. Second, isolated animal tracheobronchial epithelium strips were used for in vitro studies.

Kotin et al. (3474) have written that during study



by the first method, one initial response of the exposed epithelium was an apparent excitation, as manifested by an increased rate in the movement of particles. In response to a few specific irritants, however, they could not detect this primary effect. Exposure to these was followed by a period of decreased activity that, if allowed to persist, often resulted in total cessation of particle movement. Prolonged or intense exposure was followed by limited and delayed recovery. They found that total ciliary paralysis could be maintained for a considerable length of time after which partial recovery was still possible. They also found a considerable degree of parallelism between alterations in physiological functions and cellular abnormalities.

Exposure of the respiratory tract to irritants also resulted in an increase in mucous secretion. In addition, an increase in the number of and activity of goblet cells (mucus-producing cells) was the first histological change noted. This increase progressed until there was almost complete replacement of the normal epithelium by an overgrowth of goblet cells. Thereafter pools or lakes of mucus were formed in the epithelium, and finally, the mucous lakes emptied into the lumen (which is defined as the passageway of a tubular organ, such as a gland or a blood vessel) of the tracheobronchial tree, with complete epithelial desquamation down to but not including the basal cells.

Kotin et al., characterize this phenomenon as

"of considerable interest in that it represents a step in the pathogenetic sequence in which compounds that are not in themselves carcinogenic, theoretically facilitate the biological activity of compounds that are presumably endowed with the property of inducing cancer in the respiratory tract".

Adverting to what they call the almost universal finding of soot-laden lungs in urban residents at autopsy, they suggest that that finding might be explained first, by the action of pulmonary phagocytes in the ingestion of the particulates and second by the method whereby soot may be abnormally retained in the respiratory tract. They conducted an investigation to learn the following:

"(1) if carcinogenic hydrocarbons remain unaltered subsequent to their deposition on the respiratory epithelium or if they change qualitatively or quantitatively; (2) if any changes that might be demonstrated are associated with the activity of exogenous substances (reactive atmospheric pollutants) or endogenous factors (metabolic degradation); and (3) if a relationship exists between the amount of soot and carcinogenic hydrocarbons recovered from human lungs and the presence of 'preneoplastic' morphological changes or overt lung cancer."

Their study was conducted using 3, 4-benzpyrene and human lungs obtained by autopsy as soon as possible after death. Of all the aromatic polycyclic hydrocarbons present, pyrene alone was found to be capable of quantitation. The authors' inability to detect the others, particularly 3, 4-benzpyrene, raised the question whether the absence of these compounds

was due to the experimental methods used or whether it represented their actual fate in the human being. Addition of known amounts of 3,4-benzpyrene to samples of lung tissue during the course of experiments and detection later of the presence of 3,4-benzpyrene suggested that its absence in the untreated lung was due to factors other than methodology. Additional evidence supporting this conclusion resided in the fact that carotenoids (long chain, highly unsaturated compounds) normally present in lung tissue were identified throughout the entire extraction procedure, whereas their extreme susceptibility to oxidation suggests that 3,4-benzpyrene, a less labile compound, would have survived the analytical method used.

The size range of the particles of soot recovered from the lungs were in their opinion in the range from which 3, 4-benzpyrene could be readily eluted.

Histopathological examination of sections of respiratory epithelium removed from the lungs frequently revealed hyperplastic and metaplastic changes, which were most frequently seen at the arborizations and other impingement sites in the tracheobronchial tree. Attempts to establish a correlation between the amount of soot recovered from the human lungs and the presence of metaplastic or neoplastic changes were unsuccessful.

Kotin et al. note that particles settling on the

ciliary stream are immediately set in motion with movement sufficiently rapid to make elution and local carcinogenic stimulus to the tracheobronchial tree unlikely to occur. The damage is done, according to Kotin et al., only when the ciliary-mucus defense barrier is broken down. Carcinogenic particles inspired more deeply into the pulmonary parenchyma as far as the alveoli are ingested by the macrophages in the lung. Phagocytosis is effective in removing these particles which then may ultimately be deposited by their entry into the systemic lymphatics or by being advanced to the level of the mucous stream.

Kotin et al. express the opinion that physical factors play a significant role in the deposition of particulate matter in the respiratory tract. Thus, a large portion of inhaled soot particles are arrested in the mucous membranes of the nose, accessory nasal sinuses, pharynx, and oral cavities. At the other end of the scale, exceedingly small soot particles remain suspended in tidal air except for the small amount of ultra-microscopic particles that are precipitated by Brownian movement. Experiments have been conducted, which the authors mention, describing the retention of particulate matter in the lung in relation to particle size and correlating the location of particulate deposition with specific sites in the tracheobronchial tree.

The elution of carcinogens by appropriate organic

solvents or plasma proteins is, according to the authors, also related to the size of the particle on which the carcinogens are adsorbed. Thus, aromatic polycyclic hydrocarbons can be readily eluted from soots of very small particle size. Generally, as particle size increases, the aromatic polycyclic hydrocarbons are released more readily and in larger amounts.

8. Sanderud

In five publications released from 1956 to 1958 reporting the results of an extensive investigation of squamous metaplasia of the respiratory tract epithelium, Sanderud made numerous interesting observations (1281, 2652, 2880, 3193, 3767).

The first paper (1281) was concerned with a study of 73 autopsied cases of uremia in 44 males and 29 females. Extensive metaplasia of the respiratory tract epithelium was noted in 47 of these cases (32 males; 15 females). The author admitted that in the older patients some type of chronic irritation, such as tobacco smoke and air pollution, may have played a role in the cause of the metaplasia. However, five cases were noted of young patients (males, 17, 22 and 31 years of age; females, 18 and 35 years of age) with metaplasia in several locations; chronic irritation was ruled out in these because of the youth of the patients. Consequently the author expressed the belief that the uremia

interfered with the metabolism of Vitamin A and thereby led to epithelial metaplasia in the respiratory tract.

The remaining four papers presented by Sanderud formed a series. They were all published in 1958. The main topic was, of course, squamous metaplasia of the respiratory tract epithelium and the various subheadings were as follows:

1. Incidence, Age and Sex Distribution (2652)
2. Relation to Tobacco Smoking, Occupation and Residence (2880)
3. Relation to Disease (3193)
4. Relation to Bronchial Carcinoma (3767)

The first paper (2652) presented considerable background for the investigation and cited numerous early references each involving relatively few subjects. The definition employed by Sanderud for squamous epithelial metaplasia was as follows:

"By squamous epithelial metaplasia of the mucous membrane of the trachea and bronchi, is meant a change of the ordinary ciliated, columnar epithelium \* \* \* to epidermis-like epithelium, stratified in at least 3 distinct cell layers \* \* \*."

Since the results presented by Sanderud in these four papers are based on one sample it may be appropriate at this point to outline his sample in some detail.

"The material \* \* \* was collected from autopsy cases at The Gade Institute during the period January 1954-January 1955. Autopsy cases at this laboratory are received from the various departments of Haukeland Hospital, Bergen

University \* \* \* a general hospital for the city of Bergen and surrounding communities. Only to a minor degree are selected patients received from W. Norway \* \* \*.

95 per cent of the deceased or 500 cases were autopsied during the period the study covered, and material from over 300 of these were prepared. Sections were taken from the respiratory tract for microscopic examination.

To begin with, many of the preparations had to be rejected as the epithelium was too poorly preserved [cf. Auerbach et al., supra].

Preservation \* \* \* we succeeded in preparing the material most satisfactorily by injecting 10 per cent formalin into the trachea and bronchi as soon as possible after death, and in any case before 10-12 hours had elapsed post mortem \* \* \*. Unfortunately some cases of bronchial carcinoma had to be rejected \* \* \* but in the 214 cases presented, the mucous membrane of the whole bronchial tree was well preserved for histologic evaluation.

Age and Sex \* \* \* to obtain a suitable division of material in the various age groups only 15 of 100 still-born and new-born cases were included \* \* \* and in short (holiday) periods only individuals under 60 years of age were examined \* \* \* the final figure was 214, comprising 124 males and 90 females.

The sections for microscopic examination were taken from representative areas of the bronchial tree in the following manner: sections were removed from 11 different areas of the respiratory tract \* \* \*. The areas [were] numbered 1-11 (hereafter referred to as 'localisations' \* \* \*).

The number of metaplasia findings is not related to the number of blocks or slides but to the number of localisations. Even if seen in several slides from different paraffin blocks, metaplasia was only recorded once if these blocks and slides originated from the same localisation \* \* \*."

Sanderud (2652) observed that the metaplasia in the total sample was 49.5% (106 of the 214 cases). The

relatively high general incidence of metaplasia findings in this series was, in his opinion, partly attributable to the methodology employed. Metaplasia was observed more significantly in adults over 20 years of age (59.1% of the 169 persons aged 20 years and over showed metaplasia) than in the 45 younger persons. Of this latter group, only 13.3% showed any metaplasia, and omitting the 15 still-born and new-born cases the significance was not appreciably altered. With respect to the differences in the sexes, 70 of 100 men (70%) and 30 of 69 women (43.5%) revealed metaplasia. When the grading of the metaplasia was considered according to its extension in the bronchial tree and to the relative intensity of the morphological picture, the disparity between the incidence in the two sexes was greatly accentuated.

Before proceeding to the second paper presented by Sanderud, some of his comments on the work of others will be noted. He referred, for example, to observations of metaplasia in children. He also noted studies indicating a high incidence of metaplasia in persons suffering from "grippe". The work of Wittekind and Struder (724, 2046) on the relationship between bronchitis and metaplasia was reviewed (see, infra) as was the study of Weller (see, infra).

In the second paper, Sanderud (2880) investigated the occurrence of squamous epithelial metaplasia of the respiratory tract in the same 214 subjects in relation to



tobacco smoking, occupation and residence. The incidence of metaplasia was considerably higher in smokers (80%) than in nonsmokers (54%) when only the male population was considered. Extension of the metaplasia was greater in cigarette smokers than in nonsmokers. Sanderud also reported that there appeared to be more extensive metaplasia in proportion to the amount smoked, although the group considered in this respect, i.e., the cigarette smokers, was relatively small. The consumption of up to 35 g. (which is approximately 2 packs of cigarettes) of tobacco per week did not appear to have any significant effect on metaplasia.

The difference in the incidence of metaplasia in men (70%) (cf. 2652) and in women (43.5%) might, according to Sanderud, be due to a certain extent to the difference in smoking habits since only 4 of the 69 women smoked. The incidence of metaplastic findings in male and female nonsmokers was almost equal, namely 54% and 41% respectively. The author concluded that these observations with respect to nonsmokers in the sample and the relatively high incidence of metaplasia in this group obviously indicated that causes other than smoking played an important role in the production of squamous epithelial metaplasia of the respiratory tract. However, he did stress that smoking seemed to be "an important factor in producing squamous epithelial metaplasia" in the respiratory system. He briefly alluded to the investigations

2025018524

of Auerbach (870, 870-A, 1204-A) and Weller (721) on the relationship between smoking and metaplasia and between bronchitis and metaplasia.

Consideration of occupation in relation to metaplasia led Sanderud to conclude that metaplasia "was liable to occur more often in men engaged in 'dusty' work (79%) than in 'professional' workers (69%) or in 'open air' workers (51%)". The sample here was small.

With respect to place of residence, it was considered that residence in a "dusty" area might contribute to increasing one's disposition to squamous metaplasia of the respiratory tract epithelium.

The third study reported by Sanderud (3193) related his findings of squamous metaplasia with different diseases. He observed extensive metaplasia in cases involving myocardial infarction and commented that "cigarette smoking has possibly been of significance for both metaplasia and disease in this group". In cases of acute and chronic pulmonary diseases, e. g., bronchopneumonia, chronic bronchitis, bronchiectasis and pneumonia, metaplasia incidence and extension were only slightly greater than in the control group. In this study, as noted in a previous one (1281), Sanderud observed extensive metaplasia in 30 cases of uremia in this series of 214 subjects. He interpreted these findings as support for the view, expounded in his first paper (1281), that a connection existed between

2025018525

squamous metaplasia of the bronchial epithelium and uremia.

In this paper (3193), Sanderud reiterated his opinion that "exogenous" factors are probably responsible for epithelial changes in many cases in each disease group, and he suggested that "metaplasia is often caused by a combination of various influences".

Besides the data found in his own study, Sanderud does give an excellent, if brief, review of other studies relating metaplasia with diseases of the respiratory tract and with other diseases of a nonrespiratory nature. He commented:

"Although found in acute diseases such as influenza \* \* \* bronchopneumonia \* \* \* or lobar pneumonia \* \* \*, it has generally been assumed that metaplasia of the respiratory tract epithelium is caused by a more or less 'chronic irritative' condition such as diphtheria \* \* \*, syphilis \* \* \*, lung cysts \* \* \* and whooping cough \* \* \*, and more frequently by bronchiectasis \* \* \*, chronic bronchitis \* \* \* and tuberculosis \* \* \*."

Mention was also made of observations of metaplasia of the bronchial epithelium in fibrocystic disease of the pancreas, in Vitamin A insufficiency (such as may arise in acute alcoholism) and in cases of chronic kidney disease (cf. 1281).

In the fourth paper in the series, Sanderud (3767) analyzed his autopsy material from the 214 cases with a view to the relation between squamous metaplasia and bronchial carcinoma. No great similarity was found between the age distribution of the subjects with respect to metaplasia and

carcinoma. The sex ratios for squamous metaplasia and bronchial carcinoma, particularly squamous cell carcinoma, showed the same trends in his analysis.

He noted that metaplasia occurred very frequently and was widely dispersed compared with bronchial carcinoma, probably due to a "great many different causes of metaplasia". In this study, a prevalence of metaplasia was found in those areas of the respiratory tract where squamous cell carcinomas of the bronchial tree are most often localized. The author stressed the point that "in no case was transformation of metaplastic epithelium to malignant tumors found" in his series of 214 cases (cf. also Weller (721)).

9. Szolomajer

In 1959, Szolomajer (3809) presented the results of an investigation of the morphological changes in the tracheobronchial mucosa of the residents of Cincinnati and its environs. He studied slides taken from the trachea and bronchi of 81 pairs of human lungs derived from the two largest hospitals in Cincinnati, and has recorded the morphological changes in the tracheobronchial mucosa. His purpose was to determine whether or not there is a statistical association between the incidence of squamous metaplasia in the tracheobronchial tree and the inhalation of environmental pollutants or tobacco smoke, on the assumption that squamous

metaplasia may be a forerunner of bronchogenic carcinoma as it is known to be of squamous cell carcinoma in the uterine cervix (Cf. Greene (2075-A)).

He concluded that the likelihood of squamous metaplasia is in direct proportion to the degree of air pollution, being several times higher in the strictly urban population of both sexes than in suburban residents. With regard to cigarette smokers, he found there was a significantly greater severity of squamous metaplasia in males who smoked 10 or more cigarettes a day for longer than 10 years; other smokers showed the same average extent of metaplasia as the nonsmoking population. No correlation was found between smoking and metaplasia among females, but there was a correlation between apparent exposure to air pollution and metaplasia.

Anthracotic pigmentation was, according to Szolomajer's observations, a reflection of the relative degree of air pollution to which the deceased had been exposed over certain periods of time; such pigmentation was not deemed to be a reliable index of squamous metaplasia of the tracheobronchial tree. There appeared to be no relationship between the number of cigarettes smoked in a lifetime and the amount of carbon pigment in the lungs and lymph nodes.

Certain occupations, especially those which involve exposure to dusts, fumes, vapors and hot steam, showed a high incidence and severity of squamous metaplasia, but

VI-A-44

2025018528

Szolomajer declined to draw any definite conclusions from this in view of the relatively few cases of this kind investigated.

An almost doubled incidence of pathological change of the kind studied was observed among the males of the poorer classes of urban dwellers, whereas the females showed a three-fold incidence over those of the economically superior groups.

Szolomajer described in detail the morphological and topographical differences among persons exposed to air pollutants alone, to cigarette smoke alone, and to both. Brief descriptions of his findings follow:

(a) Goblet Cell Hyperplasia and Hypertrophy

These changes were more frequently seen in the urban residents and, according to the author, appear to be associated with general air pollutants rather than with cigarette smoke. They were so characteristic that Szolomajer claimed one could distinguish an urban from a rural resident by visual inspection of the tracheobronchial mucosa. Heavy cigarette smokers in this study did not show these changes to such an exaggerated degree, suggesting to him that it may not be as irritating as air pollution.

(b) Basal Cell Hyperplasia

Basal cell hyperplasia was noted frequently in

the bronchial epithelium of city residents but no significant gradation was observed with degree of urbanization, occupation, sex, age, socio-economic status.

(c) Transitional Epithelium

This change was observed in persons with a history of moderate or severe exposure to air pollutants or tobacco smoke. The incidence and severity of this change paralleled closely that of squamous metaplasia which, he says, it precedes. One difference was noted here in that transitional epithelium in urban residents seemed to arise from hyperplastic goblet cells whereas it seemed to arise from basal cell hyperplasia in smokers.

(d) Squamous Metaplasia

The distribution of squamous metaplasia was different in lungs exposed to air pollutants from those exposed to cigarette smoke. The latter shows the maximum degree of this change in the larynx, trachea and mainstem bronchi. Frequently these changes did not reach further down than the upper two-thirds of the trachea even in cases of excessive cigarette consumption.

Exposure to both factors, air pollutants and cigarette smoke, removed the more or less well-defined

topographical differences of each and the squamous metaplasia appeared over the entire tracheobronchial tree with equal frequency and severity.

(e) Papillae Formation

Papillae (finger-like projections of connective tissue into the epithelium) were found only in the mucosa of moderate and heavy smokers, and in non-smokers subjected to the heaviest degree of air pollution.

(f) Carcinoma Stimulates Proliferation of Bronchial Epithelium

A different type of epithelium was observed in patients with a carcinoma anywhere in the body. This atypical epithelium was found to some extent in 24 of 29 (83%) of the cases who died from, or were known to have, carcinoma.

With respect to his findings, Szolomajer stated:

"These data and the conclusions derived from them, despite certain hypotheses and speculations which have been advanced, are not regarded as direct evidence of the causation of squamous cell carcinoma, or even of squamous metaplasia. Rather they represent, at best, an exploration of relationships which may point the way to further investigations, whether these be directed toward the further examination of environmental factors, or, with the development of adequate techniques, to the reproduction of metaplastic and neoplastic lesions in experimental animals under precise conditions in the laboratory."



10. Weller

Weller (721) conducted a study, reported in 1953, very similar to that described by Sanderud. Weller's sample consisted of 128 unselected autopsies of persons ranging in age from newborn to 86 years. In each case, 21 representative sections of the trachea and large and small bronchi were taken for histological examination. In the 128 autopsies, 41 cases (32%) revealed metaplastic epithelium. The author divided these into two groups; one consisting of 16 cases of squamous metaplasia (defined as indicating a change to stratified squamous epithelium), the other consisting of 25 cases of transitional metaplasia (defined as indicating a change to stratified epithelium consisting of slightly irregular cuboidal and occasional low columnar cells with no intercellular bridges).

No metaplasia was observed in the 6 infants in the sample, aged under two years. In the 13 to 40-year age group, 7 of 18 cases (39%) revealed metaplasia of the types described above; in the 41 to 86-year age group, 34 of 104 (33%) revealed this metaplasia. These data indicate that metaplasia appears at least as frequently in the young to middle age group as it does in the older group. (This fact would be rather difficult to reconcile with the smoking-lung cancer theory since lung cancer occurs predominantly after age 50). Weller found that the male:female ratio of

metaplasia expressed in percentages observed in each group was 36:20.

The highest incidence of metaplasia (71%) was noted in the primary lung cancer cases; the next highest incidence (41%) was found in those patients with chronic inflammatory lung disease. Weller stressed, as had Sanderud, that in no instance was epithelial metaplasia noted that appeared to be undergoing, or to have undergone, neoplastic change.

11. Wittekind and Struder

Wittekind and Struder (724, 2046) in 1953 reported the results of a study of the bronchial tree in 109 autopsy cases, 42 of which involved bronchial carcinoma. The bronchial tree was fixed in situ using formaldehyde within 1 to 5 hours of death. In each case, the bronchial tree was examined histologically by taking a series of sections and preparing slides therefrom. The authors noted the relationships between epithelial metaplasia, chronic or regressive bronchitis, and between the nature and the extent of epithelial metaplasia and the various stages of regeneration of wall layers involved. Statistical analysis of the findings failed to reveal any parallelism between the frequency and extent of epithelial changes and the use of tobacco. It is of interest to note that the authors considered the number of cases under investigation to be too small to warrant any definite statistical

conclusions.

They (2046) did note, however, that there were more heavy smokers in the carcinoma group than in the control group. Microcarcinomas of the bronchial tree were found at some considerable distance from the primary tumor. This was interpreted as evidence of primary multicentric carcinogenesis. Wittekind et al. thought that there was no histological relationship between epithelial metaplasia and bronchial carcinoma. They also considered chronic bronchitis as a conditioned carcinogenic factor, much in the same category as tobacco smoke.

#### 12. Some Recent Studies

Recently, Ide et al. (3667) compared the histopathology of tracheal and bronchial epithelium of smokers and non-smokers.

Materials were taken at autopsy within 6 hours after death from men free from any evidence of cancer. The age range was from 30 to 88; the average age was 62. Histories as to smoking were taken from the patients before death or from close relatives. Cigar and pipe smokers were not included. Six groups were distinguished: (1) 23 nonsmokers; (2) 4 non-smokers with pneumonia; (3) 31 light smokers; (4) 19 light smokers with pneumonia; (5) 12 heavy smokers; and (6) 4 heavy smokers with pneumonia.

In both tracheal and bronchial epithelium it was

VI-A-50

2025018534

found that:

(1) The thickness of the epithelium increased in light and heavy smokers with and without pneumonia as well as in nonsmokers with pneumonia.

(2) The length of cilia decreased in light and heavy smokers as well as in nonsmokers with pneumonia. The percentages of cells ciliated were distinctly higher in nonsmokers free from pneumonia than in any of the other 4 groups.

(3) The percentages of goblet cells increased in light smokers and decreased in heavy smokers. In pneumonia, there was an increase in the nonsmoker and light smoker, followed by a decrease. The deep glands were increased in light and heavy smokers and slightly, perhaps, in pneumonia.

(4) Squamous metaplasia and basal cell hyperplasia, present in nonsmokers, were greatly increased in nonsmokers with pneumonia. Basal cell hyperplasia was about equal in the tracheas and bronchi of heavy smokers, nonsmokers and heavy smokers with pneumonia. In smokers without pneumonia, squamous metaplasia and basal cell hyperplasia were more numerous in light smokers, and still more numerous in heavy smokers, than they were in nonsmokers.

(5) Atypical cells and mitotic figures exhibited similar percentages in tracheal and bronchial epitheliums of nonsmokers, light smokers, heavy smokers and nonsmokers

with pneumonia. For example, the large binucleated cells numbered in the trachea 0.98, 1.22, 11.62, and 2.82 in non-smokers, light smokers, heavy smokers, and nonsmokers with pneumonia respectively; in the bronchi, 1.13, 1.37, 11.81, and 2.46 in the same groups of cases.

Almost the only difference between the responses of tracheas and bronchi was that squamous metaplasia was more frequent in the tracheas than in the bronchi of light smokers, nonsmokers with pneumonia, and light and heavy smokers with pneumonia. Carcinoma-in-situ was not noticed. The reasons for the failure of tracheal epithelium to exhibit a similar increase in cancer development to that of bronchial epithelium in response to the great increase in cigarette smoking are discussed.

Cunningham et al. (3578-A) recently extended the findings of Chayen et al. (3571) on hyperplasia and metaplasia in the bronchial epithelium in relation to the smoking habits of the subjects studied.

Andrial (4022) studied tracheal and bronchial squamous metaplasia in influenza victims. He conducted an analysis of 52 post-mortem cases that died from influenza with Basel in 1957. Epidermalization of the tracheobronchial epithelium was observed in 27 cases; the number might have been greater if serial sections of trachea and bronchi had been taken. The series consisted of 37 males; 15 females.

Squamous metaplasia was noted in 24 (65%) of the males and in 3 (20%) of the females. The ages of the victims were mostly in the 50-90 range; but metaplasia was observed in a 2-month old infant and in three patients, age 11-30.

With respect to these tissue changes in the lung due to influenza and their relationship to bronchogenic carcinoma in surviving, the author noted that there had been no rise observed in Iceland in lung carcinoma to parallel the increase in other countries in spite of the influenza epidemic of 1918-1919.

VI-A-53

2025018537

B. Experimental Carcinogenesis

Berenblum (32) has written an excellent review of the literature (citing some 500 papers) describing the contribution of experimental carcinogenesis to tumor pathogenesis, i.e., the neoplastic response of tissue to the action of carcinogenic agents. While not strictly within the scope of this memorandum, brief mention of Berenblum's review is worthwhile because of the insight he gives into the complexity of the problem of pathogenesis and the seemingly endless contradictions arising from the many experiments conducted.

Berenblum points out that experimental induction of a tumor is a relatively simple procedure, although the ease and speed with which the effect is produced varies with the species and strain of animal. He writes that the method involved, whether by repeated applications to the skin, by one or more injections, by continued feeding, or by a more elaborate procedure is detailed partly by the desired site of action and partly by the kind of carcinogen used, and that there are two patterns of carcinogenic action: one, which takes place at the site of administration of the carcinogen, and the other, which occurs remotely in some specific organs or tissues. Genetic factors also influence carcinogenesis, as is evidenced by the fact that neoplastic response varies with the species used. For example, the commonly

VI-B-1

2025018538

accepted pattern of response to skin carcinogenesis, in decreasing order, is the mouse, rabbit, rat, fowl and guinea pig. There are exceptions, however. While coal tar is highly carcinogenic for skin both in the mouse and rabbit, 3,4-benzpyrene (one of its constituents) is potent for the mouse but weak for the rabbit. Certain other tar fractions are very potent for the rabbit but not for the mouse. When tested for sarcoma production by subcutaneous injection, the order for species response is quite different from that for skin application. The rat develops subcutaneous sarcoma even more readily than the mouse, and the fowl are also highly responsive. Even the guinea pig readily develops sarcomas provided the dose injected is large; on the other hand, Berenblum points out, the rabbit fails altogether to respond to subcutaneous injections of a carcinogen even though it is one of the most susceptible to skin carcinogenesis. Berenblum summarizes his conclusions on genetic factors:

"1. Genetic factors influence the response to extrinsic carcinogenic action, the genetic differences being, on the whole, more pronounced with respect to remote than to local carcinogenesis.

2. As is the case with spontaneous tumor development, the genetic influences on induced carcinogenesis operate independently on the different tissues of the body.

3. In view of such genetic differences in response, and because of the absence of any

VI-B-2

2025018539



correlation in respect of the different tissues toward one and the same carcinogen, the term 'carcinogenic potency' can have no absolute value, and cannot, therefore, be correlated quantitatively with other (physical or chemical) properties which the carcinogens may possess \* \* \*."

Berenblum writes that age, sex, pregnancy, castration and other forms of hormonal influence play an insignificant role in determining the response to carcinogenic action. There are some cases where the hormonal influence plays an insignificant role in determining the response to carcinogenic action. There are some cases where the hormonal influence is important, however, and even decisive.

Dietary factors influence carcinogenesis, either with respect to certain types of tumor induction or carcinogenesis in general. Similarly, the choice of solvent in experimental carcinogenesis will have a distinct factor on the outcome, and irritation has been found to be a factor.

It has been shown that croton oil is a powerful promoting agent for the mouse, giving rise to tumors when repeatedly applied to skin which had been previously treated with a carcinogen for eight weeks, or even once only. Yet, croton oil by itself is not carcinogenic, and it has been found that when it is applied for 26 weeks before treatment with the carcinogen, tumor production is not accelerated. Berenblum comments that the fact that croton oil can complete the carcinogenic process but cannot initiate it indicates

that the initiating and promoting phases of carcinogenesis have independent mechanisms.

The three most striking features of the initiating process, according to Berenblum, are its specificity, its apparent speed of action (being brought on after a single application of a carcinogen), and its irreversible nature (the anticipated tumor yield being realizable even when the croton oil treatment is delayed for 43 weeks). These three features are also characteristic of a gene mutation. The main weakness of the original somatic cell mutation theory of cancer, Berenblum says, was the discrepancy between the remarkably slow evolution of tumor production and the instantaneous nature of a mutation. The two-stage mechanism of carcinogenesis might be said to give this theory a new lease on life, by attributing only the initiating stage of carcinogenesis to a mutation. Berenblum writes that while the mutation hypothesis remains the most attractive and plausible explanation of initiating action, it cannot yet be said to have been established. All the known promoting agents are irritants, and as irritation can be defined as "unphysiologic stimulation which, being potentially destructive, elicits a continued state of reparative hyperplasia", the simplest explanation for the mechanism of promoting action would appear to be that continued cellular proliferation, of a nonspecific character, was responsible

VI-B-4

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for and encouraged the dormant tumor cells to acquire the properties of a growing tumor. Berenblum says that this plausible hypothesis became untenable, however, after a result of further experiments showing, for example, that many irritants which were as effective as croton oil in eliciting epithelial hyperplasia nevertheless failed to function as promoting agents, or else functioned as promoting agents for some species but not for others, despite the fact that cellular proliferation developed in them all. These and other experiments, according to Berenblum, not only argued against hyperplasia as a factor (cf. the studies of Chang, Auerbach, etc.), but pointed to the possibility that changes in the subepithelial tissues might be responsible for promoting action. Parenthetically, this is suggestive to us of an endogenous rather than an exogenous factor.

The possibility that changes in the subepithelial tissues might be responsible for promoting action, Berenblum says, has been suggested in the past. For example, hyperemia (a congestion of blood in a part) has been credited with playing a part in carcinogenesis, but Berenblum thinks that it has been unjustifiably implicated. On the other hand, he points to experiments suggesting that ischemia (a deficiency of blood in a part), with or without accompanying fibrosis (a condition marked by increase of interstitial fibrous tissue),

may play a part in the promoting action, and states that it remains an open question.

In discussing the histogenesis of preneoplasia, Berenblum flatly states that it has not been established whether the morphological features of the so-called precancerous lesion (hyperplasia, dyskeratosis, fibrosis, etc.) are themselves preneoplastic elements, or whether they are incidental changes accompanying the specific neoplastic process. Morphological evidence of clinical material has often been interpreted, says Berenblum, as supporting the "field effect" hypothesis, which postulates that the whole of the hyperplastic zone is somehow implicated in the neoplastic process. He points out that an equally strong case can be made from morphological studies for the contrary hypothesis of the "single-cell origin of cancer". Berenblum's comments on these two hypotheses, quoted below, are of interest, particularly in view of his suggestion that metabolic studies of preneoplastic tissues (such as done by Auerbach, Chang, etc.) would be of limited interest if the dormant tumor cell hypothesis is the correct one:

"The problem is no less perplexing in experimentally induced 'preneoplasia,' for though the morphological changes can here be followed from the outset, with the reasonable assurance that tumors will eventually arise in the precancerous tissue, these tumors, too, are invariably focal in origin, while the preceding hyperplastic changes are diffuse, affecting the whole treated zone. The functional concept of the two-stage mechanism of

VI-B-6

2025018543

carcinogenesis, described in the previous section, is at variance with the field effect hypothesis, and presupposes, rather, that preneoplasia consists of isolated dormant tumor cells, lying hidden, throughout the long latent period, among a mass of non-neoplastic cells, the latter having undergone nonspecific reparative hyperplasia in response to the irritative effects which carcinogens share with noncarcinogenic irritants.

The distinction between the field effect hypothesis and that of dormant tumor cells, is fundamental, and the implications are far-reaching. It is clear, for instance, that if the dormant tumor cell hypothesis is correct, then metabolic studies of preneoplastic tissues \* \* \* would be of tangential interest only, since the values obtained would merely reflect the nonspecific side effects. Indeed, if a metabolic pattern, believed to be characteristic of tumor tissue, were also found in the stage of preneoplastic hyperplasia, that could be taken as evidence against its specificity for neoplasia, since it is inconceivable that the effect of a few single cells would be recognizable in the overall metabolic picture."

Possible explanations for the meaning of hyperplasia have been offered in various experiments reviewed by Berenblum, such as, that hyperplasia resulting from carcinogenic action is a secondary (reparative) response to injury, but no definitive conclusion appears to be tenable on the basis of these experiments.

Berenblum concludes that the two-stage mechanism of carcinogenesis with the concept of dormant tissue cells being induced by initiating action and converted into growing tissues by promoting action, represents a working hypothesis of tumor pathogenesis, although he hastens to add that many aspects of this mechanism are not understood and there are

VI-B-7

2025018544

several collateral findings which seem to be conflicting. In any event, he says, even if ultimately confirmed, the hypothesis could never claim to cover the whole range of tumor pathogenesis.

Berenblum seems to characterize the step by step sequence visualized by workers such as Auerbach and Chang, from hyperplasia to benign tumor to malignant tumor, as somewhat outmoded, for he states in the conclusion to his review:

"The contrast between the classical and the modern ideas about phases of tumor development, represents a decided change in outlook on the whole problem of tumor pathogenesis. In place of the formerly conceived transition from precancerous hyperplasia to benign tumor to malignant tumor, new ideas have emerged about dormant tumor cells, converted by promoting action to conditional growths or tumors remaining for long in a responsive stage, but later undergoing an irreversible change into a stage of progression or biological autonomy."

Whereas the number of investigations conducted to determine the response to carcinogenic agents of the cellular components of mammalian respiratory tissue is somewhat scanty, the early response of mouse skin to carcinogenic action has been described by a great number of investigators. Berenblum (32) has summarized these latter observations as follows:

"The changes include considerable thickening of the skin, with a matt rather than a shiny surface, and rapid development of alopecia associated with degeneration of the skin appendages, followed by cycles of partial regeneration; hyperplasia of the surface epithelium, with 'differentiation' toward a more stratified type; progressive swelling of the epidermal cells, with variations in size of the cells and their nuclei, nuclear distortions and

hyperchromatism, and an increase in mitotic and amitotic divisions; a higher nuclear-cytoplasmic ratio, with accentuated prominence of nucleoli; evidence of cytoplasmic degenerations (vacuolation, hyperchromatic staining, perinuclear accumulation of lipoids, etc.), but with a considerable capacity for recovery as indicated by the relative absence of cellular necrosis; changes in the subepithelial tissues, consisting of swelling and fragmentation of collagen fibers and some destruction of elastic fibers, later followed by replacement of fine, nonrefractile, collagen fibrils and (variable) formation of new elastic fibers of somewhat different structure; and dilatation of vascular and lymphatic capillaries, with a sparse accumulation of inflammatory cells."

With respect to the cellular changes observed in human lungs and their relation to lung carcinoma, Black and Ackerman (1502) stated:

"The validity of all the \* \* \* observations in the last analysis rests on the strength of circumstantial evidence. In animal experimentation, however, the whole process has been traced through identical stages from its inception in squamous metaplasia to frank carcinoma. Moller, \* \* \* for example, found that pulmonary tumors induced in mice by painting the skin with tar were preceded by 'papilloma-like modifications on the bronchi \* \* \*. The next stage was epithelial metaplasia followed by tumor formation.'"

Experimental metaplasia has been produced in rats by intratracheal and subcutaneous treatment with 1,2,5,6-dibenzanthracene (Niskanen, ACTA PATH. MICROBIOL. SCAND., Supp., 80, 1-80 (1949)). This polycyclic hydrocarbon, which produces lung cancer in rats, often produces an accompanying epithelial metaplasia.

Metaplasia has also been produced by introduction

of formaldehyde (as formalin) into the lungs of rabbits as described by Garschin and Schabad (573, 573-A) and by administration of 3,4-benzpyrene as described by Thornton and Adams (CANCER RESEARCH, 4, 55-59 (1944)).

The epithelial metaplasia observed in the respiratory tracts of persons dying from diseases attributable to Vitamin A deficiency (cf. 3193) has an interesting parallel in animal experimentation. Wolbach (J. EXPT. MED., 42, 753-777 (1925)) observed extensive metaplasia in the respiratory tracts of rats maintained on a Vitamin A-deficient diet.

Although the above experiments are of interest, our main concern is whether or not tobacco smoke can produce epithelial metaplasia in the mammalian respiratory tract. The following studies were described in 1958.

Leuchtenberger et al. reported the results of a study conducted to determine the sequence of events, from a histological, cytological and cytochemical point of view that took place in the tracheobronchial tree and lungs of mice exposed to cigarette smoke. The first publication (2573-A) was primarily concerned with the first phase of this study.

Mice (CF<sub>1</sub> albino, female) were exposed to cigarette smoke in a chamber modified from that of Essenberg (113, 115, 1615). After a short acclimatization period (usually a week) during which the mice were exposed to



several cigarettes per day, the mice were exposed to 8 cigarettes per day at hourly intervals. The mice very frequently became sick and sometimes died during the first week. This is attributed, by the authors, to the toxic effects of the cigarette smoke. However, it did occur to us that the mouse, a highly excitable species, might experience adverse effects by the manipulations themselves. At various intervals, an experimental mouse and a comparable control were sacrificed and their lungs examined. A majority of the experimental animals developed bronchitis. The bronchial epithelium from these experimental animals did not exhibit the degenerative changes observed by others in animals suffering from bronchitis induced by viral infections (cf. Straub, M., J. PATH. BACT., 45, 75-78 (1937); 50, 35-36 (1940)). In the mice exposed to cigarette smoke, the bronchitis was frequently associated with marked, often atypical, proliferative processes of the epithelium. Leuchtenberger et al. (2573-A) noted that the combination of proliferation and epithelial atypism was very similar to that reported by Auerbach et al. (870, 870-A, 1204-A) for human cigarette smokers.

The histological findings in these animals could be divided into 3 main groups; namely, no significant changes, bronchitis with mild proliferative epithelial changes, and bronchitis with marked, often atypical, proliferative changes. With respect to the latter group, the authors in summary

VI-B-11

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stated:

"The similarity between the epithelial lesions of human cigarette smokers and those of mice exposed to cigarette smoke certainly justifies a cautious optimism as to the validity of our experimental approach. It appears that the exposure of animals to cigarette smoke is a useful tool for the study of the interrelationship of cigarette smoking and cancer, in spite of the realization that this type of cigarette smoke exposure is different from that in the actual process of cigarette smoking.

With regard to the potentialities of the atypical histological changes that have been observed in the bronchial epithelium of mice after exposure to cigarette smoke, we feel that, at present, nothing can be said with certainty."

Leuchtenberger et al. commented on these observations as follows:

"Atypical basal cell hyperplasia, squamous cell metaplasia, or epithelial dysplasia, in many respects similar to what would be called 'carcinoma in situ' in man, are seen."

It should be noted at this point that many of the criticisms levelled at the findings of Essenberg (113, 115, 1615) may be applied to this study. Firstly, the apparatus was essentially that of Essenberg although the modifications were an improvement. Secondly, the treated mice were markedly discolored by the cigarette smoke; they often suffered hair loss and loss of smoothness of their coats; and either suffered weight loss or no weight gain.

Rockey et al. (2643) presented the results of a study designed to determine the early effects of the application of tobacco tar to the bronchial mucosa of dogs over a

VI-B-12

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period of 11 months. While conceding that the ideal type of experimental exposure would be the one that most closely simulated human exposure, the authors employed the technique of tracheal fenestration, viz., fabrication of surgically fashioned tracheal windows in the animal. The control animals were treated similarly in every respect with the exception that no tobacco tar was applied to the left main bronchus of the animal.

After initial exploratory studies in which 8 dogs died due to tar overdosage, 7 dogs survived. These were treated with 0.05 c.c. of tobacco tar 3 to 5 times weekly for about a week and then with 0.1 c.c. of tar 3 to 5 times weekly thereafter. These dogs lived from 178 to 320 days. Control animals (6 in number) survived 65 to 223 days. Squamous metaplasia was observed in the 7 treated animals; hyperplasia and transitional metaplasia were also observed. No squamous metaplasia was observed in the controls, although two of the controls showed the other changes. The tobacco tar was, according to Rockey et al. "remarkably effective in inducing metaplastic changes" in the bronchial mucosa. No precancerous condition was noted. The authors did note, however:

"Even as an isolated observation, however, the presence of metaplasia after application of tobacco tar is of interest. This is a material to which human bronchi are exposed, and Auerbach and his associates have called attention to the apparent association between such metaplastic change and cigarette smoking."

VI-B-13

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### C. Summary

Various changes at the cellular level, such as hyperplasia, metaplasia, etc. have been observed in the human respiratory tract.

Whereas, some investigators have advanced claims that these changes are primarily due to the effect of cigarette or tobacco smoke on the respiratory tract and have suggested that such changes are prerequisite for lung cancer, other investigators -- more objective in their approach -- have suggested that many different factors are responsible for the changes and that the relation between these changes and lung cancer is unknown. Some of the other factors involved are: Vitamin A deficiency, chronic respiratory diseases, syphilis, air pollutants arising from urbanization and occupation, myocardial infarction, etc.

Several other points arise from the studies presented. These strongly militate against the postulation of a relationship between tobacco smoking, lung cancer and the above-mentioned cellular changes. For example:

(1) Different investigators stress the importance of different cellular changes, e.g., some consider hyperplasia as important, others consider metaplasia, etc.

(2) The age distribution of the cellular changes

VI-C-1

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is different from that observed for lung cancer.

(3) The cellular changes have been observed in nonsmokers of advanced years and in persons of age less than 20.

(4) The incidence of the cellular changes, in general, is much greater than the incidence of lung cancer.

(5) Such cellular changes have been observed in sites for which cancer incidence is low, e.g., trachea.

(6) The cellular changes can be produced in animals by chemical means, by treatment with virus, by treatment with tobacco tar, or by maintenance on Vitamin A-deficient diets.

VI-C-2

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VII. THE POSSIBLE ROLE OF VIRUSES IN CANCER

[This section is adapted from one prepared for counsel by Dr. Richard E. Shope of The Rockefeller Institute for Medical Research. Dr. Shope is an eminent virologist.]

VII-1

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A. Necessity for Indirect Approach to  
Cancer Causation.

Cancer is a biological phenomenon occurring in many and perhaps all species of animals and it may be assumed that mammalian, and probably most avian, tumors are broadly comparable to those in man. The matter of directly determining the cause of cancer, however, has been limited to a study of those tumors occurring in birds and animals aside from man. The reason for this is that, by and large, each cancer is specific for the host in which it naturally occurs and can be transmitted or transplanted only to other members of the same species. In the cases of tumors of rabbits, mice or chickens, for instance, this restriction does not limit the studies of the cancer investigator and direct tests for the presence of a causative agent can be made by the inoculation of tumor material into normal individuals of the same species. In the case of cancer in man, however, this direct approach to determine a causative agent cannot be applied for reasons that are self-evident. Determination of the nature of the causative agents or factors of human cancer must be made by more indirect approaches and by applying the findings with animal cancer to man where they seem to have a possible bearing. It is because of the greater facility with which animal tumors can

VII-A-1

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be studied that our knowledge concerning the possible role of viruses in cancer is largely limited to findings with animal or bird tumors.

VII-A-2

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B. Chronological Review of Virus/Cancer Relationship.

Historically the view that viruses may be important causes of certain types of malignant disease goes a fair way back into medical history.

In 1896 Sanarelli (Centralbl. f. Bakt. Abt. I, 23, 865 (1898)) observed an outbreak of illness among the rabbits in his laboratory in Uruguay. The disease was characterized by the development of multiple tumors over the skin of the body and about the eyelids and nose and was named infectious myxomatosis. Affected rabbits died in from 8 to 14 days and on microscopical section the tumors appeared to be myxosarcomas (connective tissue tumors containing gelatinous material). Two years later, Sanarelli proved that a filterable virus caused this disease. Actually its rapid and regularly fatal course labeled it more as an acute infection than as a neoplastic process, even though the tumors considered individually did give the impression of being cancerous. Infectious myxomatosis is not considered today as an example of a virus-induced cancer, but it did serve the useful purpose of indicating, for the first time, that a virus could cause a proliferative process resembling a tumor. In 1908, Ellerman and Bang, (Centralbl. f. Bakt., 46, 595 (1908)) working in Denmark, demonstrated a virus as the cause of leukemia in chickens.

VII-B-1

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This observation did not attract the attention it probably deserved from the standpoint of cancer research because of the fact that at the time leukemia was not generally thought of as a cancerous process.

It remained for Rous (J. Exp. Med., 13, 397 (1911)) in 1911 to demonstrate the first virus-caused cancer. This was a tumor of chickens and the agent responsible for it had all of the characteristics of a filterable virus. The growths themselves were malignant tumors which metastasized and eventually killed their hosts. This discovery by Rous is generally designated as the event which introduced the era of viral tumors. Unfortunately the Rous discovery met with resistance and some people contended that because the tumors occurred in birds they could not be similar to those in mammals and hence were meaningless from the standpoint of cancer. Also it was originally thought that the very fact that an extrinsic causative agent could be demonstrated served as indication that the growths produced in chickens could not be true tumors and that, even though they looked and acted like cancers, they had to be considered as something different and apart from them. Despite the objections of some of the interpretation of Rous' discovery, it had a very profound effect and set investigators to searching for other examples of virus-caused new growths

VII-B-2

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in all sorts of animals. The list of those found has now grown to contain about 20 different tumors in nine species of animals. A list of these follows:

- 1898 Rabbit myxomatosis (Sanarelli)\*
- 1908 Fowl leukemia (Ellerman & Bang)\*
- 1911 Fowl sarcoma (Rous)\*
- 1920 Bovine papilloma (Magalhaes)
- 1932 Canine oral papilloma (DeMonbreun & Goodpasture)
- 1932 Rabbit fibroma (Shope)
- 1933 Rabbit papilloma (Shope)\*
- 1933 Fowl lymphomatosis (Furth)\*
- 1934 Canine lymphosarcoma (DeMonbreun & Goodpasture)
- 1936 Rabbit oral papilloma (Parsons & Kidd)
- 1936 Mouse mammary carcinoma (Bittner)\*
- 1938 Frog kidney carcinoma (Lucké)\*
- 1946 Fowl lymphoid tumors (Burmester et al.)
- 1951 Equine cutaneous papilloma (Cook & Olson)
- 1951 Mouse leukemia (Gross)\*
- 1953 Mouse parotid tumor (Gross)
- 1953 Squirrel fibroma (Kilham, Herman & Fisher)
- 1955 Deer fibroma (Shope, Mangold, MacNamara & Dumbell)
- 1957 Mouse leukemia (Friend)\*
- 1957 Polyoma (Stewart & Eddy)\*

(\*denotes malignant tumors)

C. Malignant Viral Tumors.

While a number of the animal tumors included above are benign tumors and do not progress to kill their hosts, some of them are malignant or have malignant potentialities. The rabbit papilloma (Shope, J. Exp. Med., 58, 607 (1933)), for instance, which starts out as an entirely benign growth eventually becomes malignant and in most cases ends up as a frank cancer (Rous and Beard, J. Exp. Med., 1935, 62, 523 (1935); Rous and Kidd, Science, 83, 468 (1936)), sometimes causing death. The mouse mammary cancer (Bittner, Science, 84, 162 (1936)) and the frog kidney cancer (Lucke, Am. J. Cancer, 20, 352 (1934); Annals New York Acad. Sci., 54, 1093 (1952)) are frankly malignant from the outset and, of course, mouse leukemia, both that of Gross (Proc. Soc. Exp. Biol. and Med., 76, 27 (1951)) and of Friend (J. Exp. Med., 105, 307 (1957)), are malignant killing processes.

D. Extrapolation to Man.

It is the demonstrated existence of the group of viral animal and bird tumors which is responsible for the sentiment becoming more and more pronounced during the past few years that viruses may also play a causative role in at least some human cancers. A question which has been raised in the minds of many is whether there is any logical or philosophical reason for considering man a species apart from other animals as regards the causation of his tumors. If viruses can serve as the cause of cancer in chickens, rabbits, mice and frogs, for instance, there seems to be no reason for believing that they might not act similarly in man. We have reached the point, it would appear, where it is somewhat unrealistic to contend that human cells are something apart from the cells of other species of animals in their capacity to react to cancer-causing viruses. After all, man is no stranger to the filterable viruses and these small extrinsic infectious agents are the cause of many of his both serious and minor illnesses (polio, measles, mumps, chicken pox, etc.), just as they are the cause of many of the diseases suffered by other animals and birds.

The position of defense counsel will be that extrapolation to humans is uncertain, but that since

VII-D-1

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plaintiffs rely on mouse painting experiments as evidence of causation in humans, they must also concede that the same argument applies to the virus theory.

VII-D-2

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### E. Latency in Some Cases.

It has been intimated earlier in this section that evidence for a viral causation of animal cancer is relatively easy to obtain merely by the administration of filtrates of animal or bird tumors to hosts of the same species. With certain of the animal tumors, however, various indirect dodges have had to be resorted to in order to demonstrate their viral causation. The mouse mammary cancer, for instance, is caused by a virus present in the milk of certain strains of mice (Bittner, Science, 84, 162 (1936)). The offspring of such strains of mice, or other baby mice foster-nursed by females of this line, acquire virus in the mouse mother's milk by nursing. However, they do not promptly come down with breast cancer - instead they remain apparently completely normal until they have reached a certain age before they show outward manifestations of cancer. Thus, in this situation, the development of cancer is dependent not only upon infection with a virus, but also upon the coincidental presence of some age-associated situation which is probably hormonal in character, and certain genetic factors (Bittner, Pub. Health Rep., 54, 1113, 1590 (1939)).

In like manner, the mouse leukemia, described by Gross, is transmitted from mother to offspring either

VII-E-1

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by way of the egg or very soon after birth and it too, like the mouse mammary cancer, does not become evident until the affected mouse reaches a certain age and probably a certain specific hormonal situation (Gross, Acta Haematologica, 13, 13 (1955); British Med. J., 2, 1 (1958)).

Thus, in these two highly fatal neoplastic diseases of mice, the causation of the actual cancer is a complicated process in which the virus plays only part of the role. They differ quite markedly, therefore, from some of the other viral animal tumors (such as the rabbit fibroma or papilloma) in which the mere introduction of virus into susceptible hosts is all that is required to set off tumor formation. No one, of course, has any way of knowing whether human cancer, if it should indeed eventually prove to be virus-caused, will resemble mouse mammary cancer and mouse leukemia in having the causative virus hormonally dependent, or whether it will resemble tumors such as the Rous chicken sarcoma or the rabbit papilloma and be caused by a virus that is directly and independently infective for the host.

VII-E-2

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F. Discovery of "Virus-Like" Particles  
in Human Cancers.

The electron microscope is a new tool by which tumor investigators can recognize viruses within cancer cells. In a number of the known viral animal tumors, tiny bodies of distinctive appearance have been seen (Gross, McCarty, and Gessler, Ann., New York Acad. Sci., 54, 1018 (1952); Dmochowski and Passey, Ann. New York Acad. Sci., 54, 1035 (1952); Gross, Ann. New York Acad. Sci., 54, 1184 (1952); Gross, Cancer, 9, 778 (1956); Dmochowski and Grey, Texas Rpts. on Biol. & Med., 15, 704 (1957); Dmochowski and Grey, Blood, 13, 1017 (1958); Benedetti, Bernhard, Oberling, Compt. rend. Acad. Sci., 242, 2891 (1956); Bernhard, Bauer, Harel and Oberling, Bull. du Cancer, 41, 423 (1955); Febvre, Harel and Arnoult, Bull. du Cancer, 44, 92 (1957)). By appropriate biological tests in susceptible animals these bodies have been identified as cancer-virus particles. The identification of virus bodies of this type in known viral tumors has led investigators to search assiduously for similar characteristic bodies in human tumors. In a number of instances, particles visible by means of the electron microscope have been found in human cancer material by Dmochowski, Gessler, et al. (Dmochowski and Passey, Ann. New York Acad. Sci., 54, 1035 (1952);

Dmochowski and Grey, Texas Rpts. on Biol. & Med., 15, 704 (1957); Dmochowski and Grey, Blood, 13, 1017 (1958); Gessler, McCarty, Parkinson and Bardet, Exp. Med. and Surg., 7, 237 (1949); Gessler, McCarty and Grey, Exp. Med. and Surg. 7, 269 (1949); Gross, Gessler and McCarty, Proc. Soc. Exp. Biol. and Med., 75, 270 (1950); Passey, Dmochowski, Astbury, Reed and Eaves, Nature, 167, 643 (1951); Dmochowski, Sykes, Grey, Schullenberger and Howe, Proc. Am. Assn. Cancer Research (abstract) 3, 17 (1959)). However, proof that these bodies actually represent the causative agents of the cancers in which they are found is completely lacking due to the fact that biological tests of their cancer-producing activities cannot be conducted (i.e., one cannot experiment with humans). These bodies have, therefore, been referred to as "virus-like" and further work will be required to tell us whether or not they actually play any role in the causation of the cancers in which they are observed.

To date, numerous attempts have been made to establish hypothetical human cancer viruses in experimental animals or in tissue culture, but in no case has success been achieved. In like manner, serological tests or work involving the use of tests such as the fixation test, the virus neutralization test or detection by use of fluorescent antibodies for immune responses has not

VII-F-2

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succeeded in establishing that a causative virus is present in any human cancer. Thus, aside from the information supplied by the electron microscope that "virus-like" bodies may be present in human cancer cells, there is yet no concrete evidence that viruses play a role in human cancer as they are known to do in certain animal cancers.

It has, of course, been established for years that viruses cause two benign tumors of man; one of these is the common wart (Ciuffo, Giorn. ital. mal. vener., 42, 12 (1907); Wile and Kingery, J. Am. Med. Assn., 73, 970 (1919)) and the other is a tumor-like condition known as molluscum contagiosum (Juliusberg, Deuts., Med. Wschr., 31, 1598 (1905); Wile and Kingery, J. Cut. Dis., 37, 431 (1919)). "Virus-like" bodies visible by means of the electron microscope have been observed in both of these tumors (Melnick, et al., Ann. New York Acad. Sci., 54, 1214 (1952)).

VII-F-3

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G. Effect of Addition of Chemical Substances.

There is evidence from animal work that certain chemical substances markedly enhance the malignant potentialities of some of the tumor viruses. Thus Ahlström and Andrewes (Ahlström and Andrewes, J. Path. and Bact., 47, 65 (1938)) found that rabbits that had received a previous injection of horizontal retort tar reacted to fibroma virus in a most unusual manner. When the virus was injected into the skin, it produced tumors at each site of inoculation which, instead of regressing, as they do in the case of normal rabbits, persisted as malignant appearing new growths for unusually long periods of time. When the virus was given into the blood stream of rabbits that had received tar, it produced a generalized and widespread growth of tumors which sometimes killed the animals. Normally the fibroma virus is completely without any grossly observable effect when given into the blood stream (Shope, J. Exp. Med., 56, 793 (1932)). The administration of tar to a rabbit thus converts it from an animal which reacts not at all to fibroma virus given by way of the blood stream to one in which the virus induces a spreading, multiple, and sometimes fatal tumor disease.

Tar also alters the reactivity of rabbits to

VII-G-1

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the papilloma virus. Thus Rous and Kidd (Science, 83, 468 (1936); J. Exp. Med., 67, 399 (1938); J. Exp. Med., 68, 529 (1938)) observed that when rabbits, to whose ears tar had been applied, were injected into the blood stream with papilloma virus, cancers appeared promptly over the areas of skin to which the tar had been applied. It should be pointed out that normal rabbits injected with papilloma virus by way of the blood stream usually develop no tumors of any sort (Shope, J. Exp. Med., 58, 607 (1933)), either benign or malignant, and the tar, as applied in the experiments of Rous and Kidd, was not of itself carcinogenic. In these experiments, therefore, it was shown that animals receiving a combination of tar and papilloma virus developed malignant cancer forthwith. Ordinarily papilloma virus applied to the skin of rabbits induces, initially at least, benign papillomas and the malignant change to cancer does not take place until some 8 to 12 months later (Rous and Beard, J. Exp. Med., 62, 523 (1938)). It is apparent, therefore, from the experiments of both Ahlström and Andrewes, and Rous and Kidd that the presence of tar in the animal materially alters the animals' reactivity to at least two tumor viruses and that this alteration is in the direction of enhancing the malignant properties of the viruses.

VII-G-2

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The late Duran-Reynals (Ann. New York Acad. Sci., 54, 977 (1952)) has similarly demonstrated the effects of chemical substances in altering the reactivity of animals to viruses. Reynals used viruses that are not ordinarily thought of as tumor-producing agents. In one set of experiments, he observed that methylcholanthrene applied to the skin of chickens that had recovered from fowl pox virus infection caused first the recurrence of fowl pox lesions, and later the development of frank cancers on the treated areas of skin. In like manner, in another set of experiments, he observed that mice recovered from infection with vaccinia virus later developed cancers at the sites of the vaccinia scars when the animals were given cortisone and painted with methylcholanthrene (Duran-Reynals, et al., Proc. Am. Assn. Cancer Research (abstract), 2, 293 (1958)). These experiments done with two different viruses indicate that, under certain conditions sometimes involving hormonal stimulation, latent viruses can be activated by a chemical substance and that cancer can result seemingly from the combined action of the chemical substance and the virus on the cells of the host (Texas Repts. on Biol. and Med., 15, 754 (1957)). It is noteworthy, in the case of Reynals' experiments, that neither the fowl pox nor the vaccinia virus are ordinarily considered to be cancer-producing agents.

VII-G-3

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Stanley (Arch. Int. Med., 102, 939 (1958))  
has speculated that while chemical carcinogens and  
physical agents, such as ultraviolet and x-irradiation,  
supposedly cause cancer by a direct effect on the  
genetic apparatus of the cell, it might be just as  
reasonable to assume that they act instead on viruses  
latently present in cells and that these activated vir-  
uses then serve as the cancer-producing entities. This  
speculation is not out of line with Reynals' findings.

VII-G-4

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### Summary

To summarize, it may be said that the case has been well proven that a number of animal tumors are caused by viruses. There is as yet no satisfactory proof that any human cancer is caused by a virus. The case for the possibility that at least some human cancers may have a virus background is based entirely upon the analogy of the similarity of certain human tumors in their development and behavior to known virus tumors of animals, and to the demonstrated presence in certain human tumors of "virus-like" bodies.

The malignancy of certain viral tumors of animals can be enhanced markedly when the viruses are concomitantly present with chemical carcinogens; also chemical carcinogens in sub-carcinogenic doses can sometimes create cancers in the presence of virus not ordinarily thought to be carcinogenic.

With respect to cross-examination material, there is a scientific school of thought that human cancer may be caused by virus. This theory is generally ascribed to the discovery by Rous (in 1911) in his study of tumors in chickens.

Since the discovery by Rous about 20 different virus-caused tumors have been found in nine species

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of animals and have been transmitted or transplanted to other animals of the same species. Some virologists believe certain animal tumors are dependent not only on virus infection but upon coincidental presence of hormonal or genetic factors.

"Virus-like" particles have been found in human cancers by use of the electron microscope. Proof that these particles are causative agents in human cancer is lacking because one cannot conduct biological tests on humans.

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VIII. OPINIONS OF GOVERNMENT AGENCIES  
AND VARIOUS MEDICAL SOCIETIES,  
GROUPS, ETC.

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Government agencies in various countries have issued statements, and various reputable medical journals have written editorials, signifying acceptance of the lung cancer-cigarette smoking hypothesis. A few of these follow:

GOVERNMENT AGENCIES

United States

The recent statements by Surgeon General Burney indicate acceptance of the cigarette-smoking lung cancer hypothesis. (2481-B)

United Kingdom

The opinions and findings of the Medical Research Council were incorporated in a lengthy report by the British Minister of Health (1454-E, 1460-B), which concluded as follows:

"Evidence from many investigations in different countries indicate that a major part of the increase (in incidence of lung cancer) is associated with tobacco smoking, particularly in the form of cigarettes . . . . the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect."

Netherlands, Sweden and Norway

Public health officials in the Netherlands, Sweden and Norway after consideration of the accumulated

scientific evidence have expressed views that there is a causal relation between cigarette smoking and lung cancer.

#### World Health Organization

In a meeting held at Louvain in 1952, sponsored by the W.H.O., the participants concluded that smoking was a major factor in the development of lung cancer.

#### Study Group on Smoking and Health (U.S.A.)

A Study Group on Smoking and Health consisting of Strong, Bing, Dyer, Lilienfeld, Nelson, Shimkin and Spain summarized their joint report (1319) in 1957 as follows:

" . . . the sum total of scientific incidence establishes beyond reasonable doubts that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung."

However, this group did also note that epidemiologic studies indicate that cigarette smoking cannot account for all cases of epidermoid cancer of the lung. They admitted that there were other causative environmental factors, the most important of which are probably various atmospheric pollutants. As in other diseases, the group conceded that various other influences, e.g., sex, nutrition, heredity, etc.,

may modify the occurrence of lung cancer.

The members of Study Group on smoking and Health were appointed by the National Cancer Institute, the National Heart Institute, the American Cancer Society and the American Heart Association. Bing has been a recipient of research grants from the Tobacco Industry Research Committee.

#### MEDICAL JOURNALS

The New England Journal of Medicine (1462-F, 1462, 1462-A, 1462-D, 1305-A), the Annals of Internal Medicine, the British Medical Journal (1454, 1454-E), and Lancet (1459-A, 1304, 1460-C) have expressed strongly in numerous editorials that the relationship between lung cancer and cigarette smoking is well-established.

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B-B-60

2025018685

APPENDIXOUTLINE OF CROSS-EXAMINATION OF EXPERT WITNESSES:  
BASIS OF OPINION

Determine the basis for the opinion that smoking a particular brand of cigarettes caused the plaintiff's lung cancer. Broadly speaking, this could be one or more of the following topics:

- (a) Statistical studies
  - (1) prospective
  - (2) retrospective
- (b) Animal experiments
- (c) Physiological studies
- (d) Presence of alleged carcinogenic agents in smoke
- (e) Personal observations

It is presumed that questions will develop for the jury what a statistical association is; what a retrospective study is; what a prospective study is; what a statistical sample is, etc.

A. Statistical Studies

1. The statistical studies merely demonstrate an association between smoking and lung cancer.
2. A statistical association per se does not

APP-1

2025018686

prove cause and effect.

"The fact that a disease is associated with some factor in the environment does not necessarily mean that the factor causes the disease \* \* \*" Hammond (2244); see also Arkin (866-B), Berkson (875), Breslow (50), Taback and Frazier (712), etc.

3. Any inference of cause and effect would have to be corroborated by experimental and population studies. Other possible explanations of the association must be ruled out.

"Supplementary evidence must be studies for consistency and to rule out other possible explanations before an observed association can be interpreted as indicating a direct cause and effect relationship." Hammord in Wynder (1134-B)

4. Illustration of associations.

(a) Factors associated with increased cigarette consumption.

(1) The decline in pneumonia, tuberculosis and influenza associated with the increase in cigarette consumption does not prove cigarette smoking prevents these diseases.

"Standardized death rates for pulmonary tuberculosis dropped from 189 per 100,000 in 1900 to 22 per 100,000 in 1950; the rates for pneumonia and influenza dropped from 214 in 1900 to 27 in 1950 \* \* \*" Hammond (650-D)

Hammond says if parallel rise proves caution, " \* \* \* then one should

APP-2

2025018687

conclude that cigarette smoking prevents pneumonia \* \* \* the decline in pneumonia paralleled the rise in cigarette smoking\* \* \*" (2244)

(2) The increase in life expectancy associated with the increase in cigarette consumption does not prove smoking caused increase in life expectancy.

Life expectancy was 47.3 years in 1900 and 69.6 years in 1958. Source: Statistical Abstracts of the United States 1958, p. 60

(b) Factors associated with increase in number of recorded cases of lung cancer.

(1) Increase in motor vehicle registrations.

"The number of motor vehicles now registered in the United States is nearly three times as great as in the base period [1924-1926] \* \* \*" Hammond (65C-D)

(2) Increase in fuel oil sales.

"Fuel oil \* \* \* annual sales now being about three and a half times as great as in \* \* \* 1924 to 1926. Soot and fumes from this source are now probably a major source of air pollution in American cities." Hammond (65D-D)

(3) Increase in motor fuel consumption.

"\* \* \* motor fuel consumption is more than five times as great" as in 1924 to 1926. Hammond (65D-D)

(4) Increase in state asphalt highways.

"\* \* \* high-type bituminous roads under state control have increased nearly sixfold since 1924 to 1926. Other types

APP-3

2025018688

of roads surfaced with asphalt and oil products have risen to such a degree that they could not even be shown on the chart without increasing the scale." Hammond (650-D)

- (5) Increase in urbanization.
- (6) Increase in industrialization.
- (7) Increase in use of rubber tires.
- (8) Increase in number of persons of  
of cancer age in the population.

See figures cited infra under Item 14.

5. The generalizations about an association between smoking and lung cancer are based on questionnaire answers obtained from small fractions of the total population.

U. S. population estimated to be about 174,064,000 on July 1, 1958. Estimate of Bureau of The Census, Department of Commerce, reported in The 1959 World Almanac, p. 257. Largest number of persons reported on is 198,926 by Dorn (3905), about .00114 of the total population.

6. The only true way to demonstrate statistically a cause-and-effect relationship between smoking and lung cancer would be to select at random a fairly large group of people, none of whom had smoked before, and assign by lot to half the group the duty of smoking for 30 to 60 years, and to the other half the duty of abstaining from smoking for 30 to

APP-4

2025018689

60 years.

This is admitted by the proponents of the theory: "Nothing short of a series of independently conducted, controlled experiments on human subjects, continued for 30 to 60 years, could provide a clear-cut and unequivocal choice between them." - referring to a choice between the theory that smoking and lung cancer have a common cause and the theory that smoking is the cause. Cornfield, et al. (3409)

7. None of the statistical studies involves groups picked at random.

(a) The Hammond and Horn group was selected by American Cancer Society volunteers from among their acquaintances (see Hammond and Horn (2534-A)).

(b) The Dorn study involved veterans holding U. S. Government Life Insurance (see Dorn (3905)).

(c) The Doll and Hill study involved British doctors (628-B).

(d) Most of the so-called retrospective studies were made of selected groups of hospital patients.

8. People in the groups studied had already decided by their own choice to be smokers or nonsmokers before the studies were begun and were not randomly designated to be smokers and nonsmokers by the investigators.

APP-5

2025018690

9. In the statistical studies no real investigation was made to get full information about other habits and living conditions, the state of the subjects' health, heredity or what physical defects and infirmities they might have had.

Cornfield, et al. (3409) state "This criticism may seem especially appropriate in view of the accepted fact that no single etiologic factor has been proposed for any neoplastic disease. The criticism may also be valid in relation to any one of the retrospective and prospective studies." pp. 184-85

10. Cancer of the lung is not a new disease; it has been recognized for approximately 150 years, long before people started smoking cigarettes.

"Laënnec described cancer of the lung in 1805 in the Dictionnaire des sciences médicales. . ." Rosenblatt and Lisa (1067)

11. If the lung cancer rate is the same today as it was before any widespread use of cigarettes, it would hardly be said that cigarettes are responsible for lung cancer.

12. If there is any validity to the theory that smoking causes lung cancer, it has to be shown that there has been an increase in the lung cancer rate during the period that there has been a

APP-6

2025018691



growing use of cigarettes in order to relate the two.

The proponents concede this: "Obviously, the case for the etiologic role of cigarette smoking would be seriously compromised if it could be demonstrated that the lung cancer rate over the past half century had been stationary, particularly after 1920 when much of the rise in cigarette consumption, instead of other forms of tobacco, occurred." Cornfield, et al. (3409)

13. Much of the increase in number of lung cancer deaths may be accounted for by the increase in the population.

14. Another reason the number of lung cancer cases has increased is because there are more people reaching the cancer age.

"In 1900 the total population of the United States was only 76 million; 44.4% were under 20 years of age, 32.2% were 20 to 39 years of age, and only 23.4% were 40 years of age or over. By 1940 the population had increased to 132 million, and 33.3% were 40 years of age or over. The changes were due to a combination of three factors: (a) a decline in age-specific death rates, (b) a decline in the birth rate (until World War II), and (c) immigration. These population trends account for a large proportion of the increase in yearly number of cancer deaths." Hammond (650-B)

15. The average life span of the population has increased steadily in the United States.

"The average was 47.3 years in 1900

APP-7

2025018692

and 69.6 years in 1956." Source:  
Statistical Abstracts of the United  
States 1958, p. 60

16. Most lung cancer cases occur in middle to late adult life.

"Bronchogenic cancer is largely a disease of later life, the peak death rate among males occurring in the age group 65-69 and among females in the age group 75-79." Hammond (650)

17. There are better methods of diagnosing lung cancer today than in the past.

18. The x-ray is more widely used and x-ray facilities more available.

19. The use of the bronchoscope is more frequent.

20. The taking of biopsies is more frequent.

21. Examination of bronchial washings is a very recent technique.

22. The use of exploratory operations (thoracotomy) is recent.

With such improved methods of diagnosis, many more cases of lung cancer are discovered than formerly.

"Considering that in males there is a large proportion of cancer sites which

APP-8

2025018693

are relatively inaccessible to ready diagnosis, \* \* \* [the increase in reported cancer deaths] probably reflects a marked degree of improvement in diagnosis of cancer at some sites, especially cancer of the respiratory system." Hammond (650-B)

23. To this extent there is not an actual increase in lung cancer, but rather an increase in the known cases of this disease.

24. Greater consciousness of lung cancer on the part of the medical profession and the public has led to finding more lung cancer cases than formerly.

For these reasons, the increase is largely apparent rather than real.

25. To determine the extent of increase in the lung cancer rate, it would be necessary to compare the rate today with the rate in the past.

26. This is impossible accurately because there were no accurate statistics for lung cancer in the past.

"The problem of accuracy of diagnosis plagues us whenever we attempt to compare death rates from cancer of specific sites in different periods of time, different countries, or different sections of the same country." Hammond (3132-A)

See also, Available Cancer Mortality Data and Some Problems in Their

APP-9

2025018694

Interpretation: United States, Vital Statistics & Special Reports, Cancer Mortality in the United States, Vol. 32, Number 2, July 18, 1950, Public Health Service, pp. 28-29

27. The collection of annual death statistics only began in 1900. At that time the area reporting deaths included only ten states and the District of Columbia.

28. Death statistics for the entire U. S. A. were first published in 1933.

Source of 27 and 28 is Section 2 of the Statistical Abstracts of the United States 1958, published by the U. S. Department of Commerce, Bureau of Census, p. 53

29. There was no separate tabulation of deaths from cancer of the lung and bronchus in the United States until 1939.

"Tabulations of death from cancer of the lung and the bronchus are unfortunately not available before 1939." Hammond (650-B)

There was no tabulation in the United States of deaths from cancer of the "bronchus and lung specified as primary" until 1949.

See Fifth and Sixth Revisions of the International List of Causes of Death.

30. Death statistics are based on death certificates which are often inaccurate as to cause of death.

APP-10

2025018695

"Cause of death as stated on death certificates is subject to error, particularly when the doctor who signs the certificate has little or no opportunity to study the patient before death and no autopsy is performed." Hammond and Horn (2534-B)

31. Lung cancer is difficult to diagnose.

"Lung cancer is relatively difficult to diagnose, but there is every reason to believe that the accuracy of diagnosis and of reporting has improved with time." Hammond (650-D)

32. Microscopic examination is necessary to confirm a diagnosis of cancer.

"Most pathologists will accept a diagnosis of cancer as being proved only when it has been confirmed by microscopic examination of a specimen of the tumor." Hammond (2244)

33. Even with microscopic verification the original site of cancer may be doubtful.

"\* \* \* even in microscopically verified cases there is sometimes doubt as to the exact primary site, especially when the disease has already spread widely by the time of first diagnosis." Hammond and Horn (2534-B)

34. Nonsmokers get lung cancer.

35. The vast majority of smokers and even heavy smokers do not get lung cancer.

Of Hammond and Horn's heavy cigarette smokers,

APP-11

2025018696

99.52% did not die of lung cancer.

36. The average life span has increased strikingly hand-in-hand with an increased consumption of cigarettes.

37. Per capita consumption of tobacco is much less in England than in the United States; lung cancer incidence in England is much greater.

"\* \* \* the lung cancer death rate in England and Wales for males was 2.1 times as high as in the United States \* \* \*

In 1956 the reported consumption per adult per annum of packeted cigarettes was 2,509 in the United Kingdom and 3,195 in the United States." Hammond (3132-A)

38. Cities of the same size in the United States where no local difference in tobacco use is known have very different rates of lung cancer incidence.

Incidence of cancer of bronchus and lung, morbidity rates per 100,000 population for males 1947:

Atlanta	13.4
New Orleans	39.1
Dallas	29.0
Birmingham	18.9

See Hueper (970-B)

39. There is a lower incidence of lung cancer in rural than in urban areas. This cannot be explained by differences in smoking habits.

APP-12

2025018697

"Mortality data from several countries indicate strongly that lung-cancer rates are much higher in cities than in rural areas, and the observation that urban males in general have higher lung-cancer mortality than rural males is undoubtedly correct\* \* \* the evidence indicates that adjustment for smoking history could account for only a fraction of this urban-rural difference." Cornfield, et al. (3409)

40. Persons in the lower income brackets smoke less than other persons, but this group has a higher incidence of lung cancer.

"The rate of smoking tends to increase with income. In each age group, the percentages of over-a-pack-a-day smokers in the middle and upper income brackets are generally substantially higher than among those with lower incomes." Tobacco Smoking in the United States in Relation to Income, Marketing Research Report No. 189, July 1957, U. S. Department of Agriculture, at p. 63

Cornfield et al. (3409) admit a greater rate of lung cancer in the lower income groups.

41. The lung cancer rate is far higher in men than in women. This disparity cannot be explained by differences in smoking habits.

Dorn and Cutler admit: "The largest sex differential for a major system of the body is found for the respiratory organs. The incidence rates are:

	Male	Female	Ratio male to female
Total respiratory tract	38.2	8.3	4.60
Larynx	7.4	.6	12.33
Lung, bronchus, pleura	29.2	6.5	4.49
Other localizations	1.6	1.2	1.33"

APP-13

2025018698

Speaking of the forms of cancer for which incidence is twice as great for males as for females, they say "A variety of etiological agents, such as tobacco \* \* \* have been suggested for these forms of cancer, but there is no established proof that any of these can account for the sex difference in incidence." Dorn and Cutler (3905-C)

42. Women have been smoking in increasing number for over 25 years. If cigarette smoking caused lung cancer, the sex ratio should tend to equalize as more women smoke more. But far more men than women still get lung cancer.

Haenszel, Shimkin and Miller (1156) refer to the " \* \* \* large-scale adoption of the smoking habit by women in the 1920 and 1930 decades." They estimate that 33% of women over 18 do or have smoked cigarettes. Of 18 million women smokers, 15 million had at one time been regular cigarette smokers. There are 55.1 million women.

43. There are wide fluctuations in the proportion of men to women getting lung cancer. Known differences in smoking habits do not explain these fluctuations.

"In 100 consecutive cases collected by Lindskog in 1938 to 1943 the ratio was 4.5 to 1, and in another series collected in 1947 and 1948 the ratio had reached 24 to 1. At Barnes Hospital the ratio in our last 150 cases has been 18.5 to 1. This shift in ratio has been noted in varying proportions throughout the country." Wynder and Graham (474)

APP-14

2025018699



44. No comparable increase is claimed for cancer in other body sites exposed to tobacco smoke, e.g.: Lip, buccal cavity, larynx, pharynx, naso-pharynx, trachea.

Ochsner would claim a parallel increase in larynx cancer, but we know of no other proponent of the theory of causation between cancer and smoking, who claims a comparable increase with lung cancer.

45. Tars from cigarettes do not cause cancer of the human skin (although they come in contact with smokers' fingers).

Hueper (970-B) says: "There is \* \* \* not a single record available of cancer of the fingers attributable to cigarette tar."

46. The statistical studies do not purport to show any comparable association between lung cancer and pipe and cigar smoking.

47. There is no proof that differences in inhaling explain the differences in lung cancer incidence among cigarette, pipe and cigar smokers.

According to Fisher (3611), the retrospective study of Doll and Hill actually shows that fewer inhalers get lung cancer.

While three studies have purported to find a higher risk among inhalers, the proponents concede that no explanation has been found for the findings

APP-15

2025018700

to the contrary of Doll and Hill.

"It must be admitted that there is no clear explanation of the contradiction posed by the Doll-Hill \* \* \* findings \* \* \*." Cornfield et al. (3409).

48. It would be perfectly logical to assume that the statistical association may be explained on the basis of some third factor causing both heavy cigarette smoking and lung cancer, e.g., a genetic, inherited or constitutional factor, the pressures of modern living or "the rate of living."

Hammond concedes that one hypothesis may be that smoking is incidentally associated with an unknown factor causing cancer. See Hammond & Machle, Mayer & Maier (1017).

"There are a number of characteristics in which cigarette smokers are known to differ from nonsmokers and presumably more will be discovered." See Cornfield, et al. (3409).

"Recently, Fisher reported that 51 monozygotic twins resembled each other more in their smoking habits than 33 dizygotic twins, thus suggesting a genetic determinant." Cornfield, et al. (3409).

49. The statistical association may be without any significance whatsoever; cancer may be caused by a virus.

50. Within the medical profession there are differences of opinion as to whether smoking causes lung cancer.

APP-16

2025018701

51. Lung cancer in nonsmokers is not caused by cigarette smoke, but by some unknown factor. There is no way of knowing whether this unknown factor was operative in the plaintiff's case.

APP-17

2025018702

A. Animal Experiments

1. It is presumed that questions will be asked to determine what, if any, data based upon animal experiments are relied upon by the expert.

2. Cancer can be induced in certain animals by exposure to many common substances such as tomato juice, sugar (glucose) and egg white.

Editorial, Am. J. of Cancer, Vol. 16, pp. 1525-1528, 1932 [Tomato Juice]; Hartwell, Survey of Compounds which have been tested for Carcinogenic Activity, 2d Ed., 1951, National Cancer Institute, at pp. 482 and 483 [Glucose]; Abstract in J.A.M.A., Vol. 144(1) 1950, p. 74 of Hartmann, "Eggwhite as Carcinogenic Factor", Oncologia, Vol. 2(4) pp. 193-252, 1949 [Eggwhite].

3. A very large number of chemical agents not related to tobacco smoke can produce cancer in mice.

"The present book lists 1329 compounds of which 322 were reported to cause malignant tumors in animals and 35 others to induce only benign ones. \* \* \* As in the first edition, the present work lists only single compounds. Such complex mixtures as tars, irradiated sterols and articles of diet are not included." Hartwell, supra, in Introduction at pp. 1 and 2.

4. Wynder admits the possibility that the mice used by him in his first experiment were of a particularly susceptible strain.

"The possibility remains that the CAF<sub>1</sub> strain of mice may be particularly susceptible

to the carcinogenic effect of cigarette tars." Wynder, Graham and Croninger (475).

5. When painted with highly concentrated tobacco smoke condensate for a prolonged period less than half of Wynder's susceptible mice developed skin cancer.

"Of 81 tarred mice, 44.4 per cent developed epidermoid cancer of the skin." Wynder, et al. (475). The animals had to be painted for about half their life span.

6. Wynder's first results have never been duplicated either in his own laboratory or by anyone else.

"The high frequency of carcinoma induction reported by Wynder et al. has not been achieved by other investigators who reported that no more than 20 per cent of animals, and usually considerably less, developed carcinoma of the skin." Cornfield, et al. (3409).

7. A number of investigators have applied highly concentrated tobacco smoke condensate to the skin of mice without producing any skin cancer.

"It is undeniable that some investigators did not obtain positive results \* \* \*." Cornfield, et al. (3409) supra.

8. Prolonged exposure of the lungs of rodents to massive doses of cigarette smoke has failed to produce lung (bronchogenic) cancer.

"Little has noted that ' \* \* \* prolonged exposure of the lungs of rodents to massive doses of cigarette smoke has failed to produce bronchogenic cancer.' This remains true at the time of this report \* \* \*." Cornfield et al. (3409).

9. Attempts to produce cancer with highly concentrated tobacco smoke condensate in experimental animals other than a few strains of mice and one group of rabbits have uniformly failed.

This can be seen in (3409).

10. Many agents shown to produce cancer of the skin in mice have not been proved to cause cancer in man.

"It is, of course, a fact that many agents shown to be carcinogenic to the skin of mice have not been proved carcinogenic to man." Cornfield et al. (3409).

11. The fact that skin cancer in mice can be produced by highly concentrated tobacco smoke condensate does not mean cigarette smoke has any effect on human lung tissue.

"Condensed tobacco smoke contains substances that are carcinogenic for mouse and rabbit skin. It does not necessarily follow that these substances are also carcinogenic for human lungs \* \* \*." Cornfield et al. (3409).

12. The basic reason is that different types of animals, different strains of the same type of animal and even different tissues (such as skin and lung tissue) in the same animal react very differently to the same agent.

"Obviously they [animal data] can only indicate the nature of a carcinogen to a specific animal strain, species and tissue. This truism applies not only to this specific instance [tobacco tar] but to all phases of cancer research. Wynder (1299-A).

APP-20

2025018705

"Direct extrapolation from one species to another is, of course, not justified."  
Cornfield et al. (3409)

13. Painting of the skin of higher types of mammals (monkeys) with substances which are known to produce cancer in mice has never produced cancer in these higher types.

This emphasizes that the reaction of mice is not the same as the reaction of types of mammals more like man.

"Some animal species, such as the rat, rabbit and dog, are much more resistant to certain chemical carcinogens than is the mouse, and vice versa, while in the monkey none of the powerful carcinogens has been shown to produce tumors." Hartwell, supra, p. 2.

14. Wynder produced about twice as much condensate as most independent testing laboratories calculate to be in cigarettes smoked under ordinary human smoking conditions.

"The average weight of the residual tar obtained \* \* \* was 9.7 gm/200 cigarettes." Wynder, Graham and Croninger (475).

50 grams per 1000 cigarettes equals 50 milligrams per cigarette.

Lucky Strike cigarettes have 31.5 milligrams of tar per cigarette according to (1829) where "Particular care was taken to recover all the tar that a human might inhale in the smoke."

APP-21

2025018706

15. Wynder admits that his smoking machine smoked at a rate "\* \* \* greater than that encountered in the average human smoking."

See Wynder, et al. (475).

APP-22

2025018707



### C. Physiological Studies

Certain investigators claim to have found cellular changes in the lining of the trachea and bronchi of smokers and of animals exposed to cigarette smoke. Auerbach, et al. and Chang, working with human tissue, and Rockey and Leuchtenberger, working with animals, found thickening of cells and in some cases changes of cell type (metaplasia). Auerbach called some of the changes he noted "carcinoma-in-situ" or pre-cancerous. He found the same changes in nonsmokers, but claimed smokers exhibited them to a greater degree. Chang, in addition, claimed to have found shorter cilia (the hair-like projections which move foreign particles out of the tracheo-bronchial passages) on the average in smokers than in nonsmokers. Hilding, working chiefly with dead cows' lungs, asserted cigarette smoke inhibited ciliary action.

It is presumed that questions will be asked to determine what, if any, data based on these studies are relied upon by the expert.

1. Cell changes observed by Auerbach cannot be proved to be caused by smoking since these changes are also present in nonsmokers.

This is evident from Auerbach's reports (870, 1204-A).

APP-23

2025018708

2. Auerbach, working with patients who had died of lung cancer and other diseases, obviously could not have made any determination whether changes found in smokers were present before the smokers began to smoke. Therefore, there is no proof that smoking caused the changes.

The same point can be made with respect to Auerbach's observation that small areas without cilia appeared more frequently in smokers than in nonsmokers.

Also, many factors such as cell changes resulting from prior lung disease could produce such deciliated areas.

"Patches of squamous metaplasia are commonly seen in human lungs that have been the seat of chronic infections or irritations \* \* \*" See Smith, Mayer and Maier (1017).

3. There is no proof that Auerbach's so-called "carcinoma-in-situ" would ever have developed into cancer.

"Certainly there are no data to indicate what proportion of these morphologically abnormal areas would progress to invasive carcinoma." Cornfield, et al. (3409).

4. Other investigators reported such changes occurring approximately as frequently in the trachea, which is directly exposed to smoke and where cancer incidence is low, as in areas of the bronchus. This clearly establishes that such changes are not "pre-cancerous."

APP-24

2025018709

"In our specimens, these epithelial lesions were developed to about the same degrees in the tracheas and bronchi. But the evidence is convincing that the incidence of tracheal cancer has not increased with the increase in cigarette smoking to anything like the increase in the incidence of bronchogenic carcinoma." Ide, Suntzeff and Cowdry (3667).

5. The Leuchtenbergers found that, while mice exposed to massive doses of cigarette smoke developed changes in bronchial epithelium, no cancer ever developed and when exposure was stopped the bronchial epithelium appeared to be restored to its normal condition.

6. Hilding's experiments on ciliary streaming using cigarette smoke were done with removed dead cows' lungs and not with living human organisms. See 965, 965-A, 965-B, 1231, 1359, 1359-A, 2256, 3655, 3655-A.

7. Hilding, who worked only with postmortem specimens, concedes that ciliary action in a living organism might present a different picture.

"It is, of course, possible that the details are different in the living organism."  
Hilding (1359).

8. Chang, working with autopsy material, obviously could not have made any determination whether the claimed shorter cilia were present in smokers before they began to smoke. Therefore, there is no proof that smoking

APP-25

2025018710

caused the alleged shorter cilia.

9. In no case is it possible to tell the cause of a particular lung cancer from examining the tumor itself. In no case is it possible to tell, by observing a particular lung tumor, whether it occurred in a smoker or a nonsmoker.

APP-26

2025018711

D. Alleged Carcinogenic Agents in Cigarette Smoke

It is presumed that if the witness bases his opinion upon the presence of a carcinogenic agent in cigarette smoke, questions will be asked to elicit the identity of such agent. Broadly speaking, these could be polycyclic hydrocarbons, particularly 3,4-benzpyrene, and arsenic. If the witness simply relies on "tars" see section on Animal Experiments.

1. The polycyclic hydrocarbons reportedly found in cigarette smoke in infinitesimal amounts are not known to cause lung cancer in man.

2. No chemical compound known to cause lung cancer in man has been isolated from tobacco smoke.

"Whether these compounds are equally involved in human pulmonary carcinogenesis is, of course, conjectural." Cornfield et al. (3409).

3. The reported amounts of these compounds in cigarette smoke are infinitesimal and are not even sufficient to produce skin cancer in mice.

"At present there is no evidence of a known carcinogen in tobacco tar in quantities large enough to account for the observed animal activity." Wynder (1299-A).

4. 3,4-Benzpyrene, reportedly seen in cigarette smoke in infinitesimal amounts, is not known to cause lung

cancer in man.

"Present animal experiments indicate that this amount of benzpyrene is insufficient to induce cancer in the experimental animal. No one can prove whether this amount of benzpyrene might have any activity in man, but on the basis of the animal data this concentration is not likely to have a carcinogenic effect on man." Wynder (1134-B).

5. The reported amount of 3,4-benzpyrene in cigarette smoke is infinitesimal and is not even sufficient to produce skin cancer in mice.

"The benzpyrene content of cigarette tar is not more than 2 p.p.m. which, according to our experiments, is not sufficient to produce the type of activity noted in our animals painted with tobacco tar. \* \* \*"  
Wynder (1299-A, 3525).

6. Arsenic is not known to cause lung cancer in man.

"In view of the years of study given this problem and the repeated failures to obtain definitive and concordant results, it is necessary to state that any role that arsenic may play in the production of lung cancer remains to be established." See Hammond and Machle in Mayer and Maier (1017).

"Human data, too, seem to indicate that the arsenic content of tobacco is unrelated to the cancer incidence, as measured on the basis of the geographic distribution in various parts of the world where the arsenic content of tobacco varies significantly."  
Wynder (1134-B).

7. The quantity of arsenic in cigarette smoke is infinitesimal.

APP-28

2025018713

"The arsenic content of our tar sample is about 35 p.p.m. Again, this is not sufficient to induce the number of skin cancers produced." Wynder (1299-A).

8. Rienhoff (3753-A) has summed up the carcinogenic action of cigarette smoke as follows:

"\* \* \* I have found that lung cancer seems to begin peripherally in the majority of cases - that is, on the outside zones of the lungs. Thus, to accept the cigarette theory, we must assume a carcinogenic agent which mercifully spares fingers, lips and mouth, not to mention the passages down to the lungs through the windpipe, or trachea, and even there does not begin to work until it has reached out to the periphery of the organ. This is a very large assumption."

APP-29

2025018714